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Cervical screening for under 25s 'has little impact'

Cervical screening in women aged 20–24 'has little or no impact on rates of invasive cervical cancer up to age 30'. Researchers say policy decisions need to take into account the underlying risk at different ages.

The research group, based at Queen Mary College, University of London, UK, collected data on 4012 women with invasive cancer aged 20–69. Two matched controls per case were selected.

Screening was associated with a 60% reduction of cancers in women aged 40, increasing to 80% at age 64, and was particularly effective in preventing advanced stage cancers. But the efficacy of screening decreased with decreasing age, even within the age range 20–34 (*BMJ 2009;339:b2968*).

The study was prompted by controversy in England following the move in 2003 to restrict invitations to women aged 25 and over. The most common harms associated with screening are the anxiety caused by abnormal test results and the trauma of treating cervical intraepithelial neoplasia (CIN) that would never have progressed; this treatment might be associated with premature delivery in subsequent pregnancies.

The lack of benefit in women aged 20–24 'is almost certainly generalisable to other countries,' the researchers said. Policy decisions might depend on the local status quo, so that where screening is already offered to this age group 'policy makers might decide to continue this policy as we have not shown that the harms exceed the benefits.

'By contrast, where screening is not offered to women aged 20–24, the lack of evidence of any benefit from screening in this age group dictates that the policy should not change.'

In future, vaccination against HPV will shift the balance still further, the researchers predicted. 'There can be no doubt that the risk of cancer in women aged under 25 who are vaccinated before exposure to HPV will be low enough to make screening at such an age unjustifiable,' they concluded.

'Serious concerns' about health evaluation methods

Methods used to determine treatment benefits in order to allocate scarce healthcare resources have been questioned by UK researchers.

They found substantial differences in the values obtained directly (usually from patients) and the more frequently used indirect methods, which are weighted according to the views of the general public.

Direct methods produced consistently higher scores (better recorded health) than indirect methods. It implies that reliance on indirect methods will result in fewer resources being allocated to life-saving treatments.

Researchers analysed 32 studies, involving 4688 respondents, which compared direct and indirect methods for a wide range of diseases. Each was classified according to whether respondents were 'current patients' (with direct experience of a certain condition) or 'hypothetical patients' (asked to imagine experiencing the condition).

Potential explanations for the discrepancy, they say, include the constraints imposed by questionnaires in indirect methods: they do not allow respondents to report potentially positive aspects of the situation – benefits from family, friends, work and recreation, for example – which would boost scores. It is also likely that the general population used to obtain the 'weighting' for indirect methods is spread across a wider age range than the typical patient populations in direct estimations. 'Young people in good health and people with diseases may have very different perspectives on the relative merits of remaining in a given health state and making a trade off involving death.'

Scores obtained from indirect methods can be converted to those from direct methods but the researchers warn that while conversion 'may be better than nothing' it 'is only partially successful.'

The different methods led to such noticeable differences that the authors concluded that priority-setting institutions should avoid using a mixture of methods for different decisions 'otherwise a motivated choice

(*continued over*)

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Sunbeds reclassified as Group 1 carcinogen

The International Agency for Research on Cancer (IARC) has moved sunbeds up to the highest cancer risk category and reclassified them as 'carcinogenic to humans' (group 1). Sunbeds and sunlamps were previously classified as 'probably carcinogenic', or group 2A.

The reclassification was made by an IARC Working Group in June 2009. The Group considered a comprehensive meta-analysis, which concluded that the risk of skin melanoma is increased by 75% when use of tanning devices starts before 30 years of age. Several case-control studies also provided consistent evidence of a positive association between the use of tanning devices and ocular melanoma.

'The characteristic genetic mutation that is caused by solar radiation has long been attributed to UVB radiation. However, the same mutation was detected in the skin of UVA-treated mice, and in UVA-induced mouse skin tumours. Thus IARC reclassified UV radiation as a whole (UVA, UVB and UVC) as carcinogenic to humans, or group 1.

The assessments are discussed in a Special Report (Lancet Oncol 2009 10:751–2) and will be published as part D of Volume 100 of the IARC Monographs (see http://monographs.iarc.fr/).

Euthanasia and palliative care 'can co-exist'

Decisions that shorten life, including euthanasia or physician-assisted suicide, are not related to lower use of palliative care and often occur in multidisciplinary care settings, say Belgian researchers.

The group looked retrospectively at 1690 non-sudden deaths within general practice in Belgium, a country with well-developed integrated palliative care provision and legalised euthanasia. They gathered data on the reported care provided in the final 3 months of life, and the end of life decisions made.

In the study, 32% of patients were at least 85 years, and 43% had cancer. Assisted dying, intensified prescribing, and continuous deep sedation without food or fluid, were more commonly decided on in the group with cancer.

The researchers found that use of multidisciplinary palliative care services was associated with a higher incidence of several end of life decisions, including decisions explicitly intended to shorten life. Furthermore, any concern that euthanasia or physician-assisted suicide might be disproportionately chosen by or for patients who do not access palliative care was not supported (*BMJ 2009; 339:b2772*).

"Life shortening and a philosophy of palliative care do not have to oppose each other; they commonly coexist," the researchers concluded.

Dr Ira Byock (Dartmouth-Hitchcock Medical Center, New Hampshire, USA) asked in an editorial, 'Was this really in question? People from both ends of the political spectrum agree on the need for unhindered access to high quality palliative care…' she wrote (*BMJ 2009; 339:b2730*).

Only 22 acts of euthanasia and physician assisted suicide were recorded (1.3% of the deaths) in the study. In Belgium, 'legalising euthanasia has not led to a high frequency of hastened deaths,' she said, but 'it would be a mistake to suggest that these findings dispel concerns about euthanasia or that they support including euthanasia within palliative care.'

'Good reasons exist for the relatively new specialty of palliative medicine to reaffirm the principle of neither hastening nor prolonging death. This stance asserts neutrality in matters about which people have deeply personal and widely divergent feelings,' she said.

She criticised the study for confounding distinct actions and intentions, for example, by not distinguishing between acknowledging that an earlier death might occur and explicitly ending a patient's life. Further descriptive and comparative research is needed in jurisdictions where life ending procedures are legal and those where they are proscribed. 'Such research must be crafted, conducted, and reported with care', she concluded.

'Serious concerns' about health evaluation methods *continued from page one*

of method might be used to distort the outcome in a preferred direction' (*BMJ doi:10.1136/bmj.b2688*).

An accompanying analysis (*BMJ doi:10.1136/bmj.b2577*) makes a more direct appeal for increased use of direct methods. 'Subjective wellbeing provides us with a means of valuing the real reduction in suffering that health technologies bring,' write researchers from Imperial College, London, UK.

The UK's National Institute for Health and Clinical Excellence (NICE) recommends that health benefits should be valued in terms of gains in quality adjusted life years (QALYs). The authors say they have 'serious concerns' about the 'quality-adjustment' recommended: 'NICE suggests asking members of the general public to think about how many years of life they would be willing to trade to avoid different states of health. The trouble is that these hypothetical preferences often bear little relation to the real experiences of those in the health states.'

'HYPOTHETICAL PREFERENCES OFTEN BEAR LITTLE RELATION TO THE REAL EXPERIENCES OF PATIENTS'

Acknowledging problems with direct patient values – which may reflect adaptation to a condition so that those who adapt are not seen to be suffering quite so much – the researchers suggest that in limited circumstances it might be more appropriate to judge health states in terms of what people can do rather than how they feel.

But the fundamental point, they say, is the evidence that public and patients' valuations do not correctly predict the degree to which health states will actually affect them. 'For the public considering moderate pain or discomfort, for example, it is difficult not to imagine that the pain will dominate their lives. In fact, this is not likely to be the case, especially over time.

'We suggest that subjective wellbeing offers a more direct and accurate way of assessing how health states impact on the lives of those most affected by different health conditions,' they conclude.

EUROFILE

Putting the EU plan into action

An EU-wide partnership to tackle inequalities in cancer prevention and control will be launched in Brussels by the European Commission on 29 September 2009. It is to decide how goals set out in the EU cancer action plan, adopted in June 2009, are to be achieved.

The plan was developed in consultation with a wide range of stakeholders, and includes targets for coordinating cancer research, collecting accurate and comparable data for benchmarking, and reducing the burden of cancer on society. It also envisages integrated national cancer plans in all EU member states by 2013.

The Commission hopes that the momentum generated by the consultation will carry over into the partnership, and it is inviting stakeholders to express their interest in taking part. The aim is to bring in people from national authorities, regulatory bodies, healthcare professionals, patient groups, civil society, the research community, the pharmaceutical industry, health insurers and academia. The tobacco industry has been excluded.

Informal discussions with stakeholders will take place in autumn 2009, with a view to setting up a formal structure that can begin work early in 2010. The present thinking is that four working groups will deal respectively with prevention, healthcare, research and data, and operate under a steering committee and forum.

'THERE'S NOTHING FRESH IN THE PLAN; IT'S JUST A TALKING SHOP'

With virtually no new funding available before 2013, the partnership will have to work with existing resources. However the Commission can generate a certain amount of leverage using 'joint actions', a legal instrument which allows it to direct funds from EU health and research programmes, and pool them with national resources. Regional development programme funding could also be used to support actions on infrastructure and training, for example.

This means that EU governments will also have to show some commitment. 'This whole enterprise depends on political will,' says Nick Fahy, head of health information in the Commission's directorate general (DG) for health and consumers. 'If it turns out that member states are not willing to put real effort and commitment into doing this, then it won't work.'

He is optimistic about what can be achieved. 'This is all innovative, all something that hasn't been done before,' he says. 'I'm hoping that, in at least one or two of these areas, we will end up actually doing something that will really surprise me.'

The action plan is most ambitious in its desire to reduce the duplication of cancer research. It sets a target of coordinating one-third of cancer research from all funding sources, private and public, by 2013. 'It has never been done before, as far as I know, in any research field. So it's quite new and it's quite brave,' says Fahy, adding that there is a broad consensus that such coordination is necessary. 'The figure is a pragmatic and slightly ambitious one on our part, [based on] what might be feasible. [. . .] What this requires is people like the cancer societies, the public funders and even industry to actually be willing to sit down and work together.'

On benchmarking, the Commission wants to have accurate and comparable data on cancer incidence, prevalence, morbidity, cure, survival and mortality in the EU by 2013. 'We have registry data for every member state of the EU of wildly varying levels of coverage, but we do have data,' says Fahy, who is convinced that the target can be reached. 'There's concern about how data are generated and used, and concerns about data protection. It's still politically difficult, [but] I'm sure we can bring together the existing structures into something that can be very effective at European level.'

The plan also seeks to reduce the burden of cancer by stepping up screening for breast, cervical and colorectal cancer to 100% population by 2013. This would provide 125 million examinations to citizens per year.

When it comes to tackling healthcare inequalities, the Commission considers a 70% reduction in the disparity between the best and worst performing member states by 2020 to be feasible. This will be supported by guidelines for models of best practice in cancer-related care which take into account national, regional and local contexts.

'THIS IS ALL INNOVATIVE; ALL SOMETHING THAT HASN'T BEEN DONE BEFORE'

The plan includes a set of actions that might be considered under each objective. However many of these – such as an EU-wide pilot accreditation scheme for breast cancer screening, diagnosis and management – are already underway, which has led to accusations that the plan is too limited in its ambitions.

'There's nothing fresh in the plan, and with no new money it's just a talking shop,' says Richard Sullivan, director of the European Cancer Research Managers' Forum.

He is particularly critical of the plan's 'naïve' approach to research overlaps. 'The co-ordination of cancer research is already being undertaken, and it will happen through the NOCI [Network of Core Institutions] and through increasing major institute-to-institute relationships,' he explains. 'Everybody is going that way.' Expecting governments to co-ordinate is not realistic, he adds. 'The federal funders are all ferociously in competition with each other and it's not in their best interests to co-operate.'

Nevertheless, ECRM will be attending the preliminary stakeholder meetings this autumn, as will ECCO. 'We are committed to play an active role in the partnership, across all the stakeholder working groups,' says public affairs manager Ingrid Van Den Neucker, 'but we still need to decide internally how that is going to happen.'

Saffina Rana
Brussels

New genetic link to ovarian cancer

Scientists have identified a single nucleotide polymorphism (SNP) linked uniquely to risk of ovarian cancer. Women carrying the DNA variation on both copies of chromosome 9 have a 40 percent increase in lifetime risk of the disease, compared to someone without the variation, they say.

An international team of scientists searched the genomes of 1,810 women with ovarian cancer and 2535 women without the disease from across the UK. They analysed 2.5 million variations in DNA base pairs, to identify the SNP on chromosome 9.

They confirmed the finding by looking at 7000 more women with ovarian cancer, and 10,000 without the disease. The lifetime risk of ovarian cancer for women carrying the variation on both chromosomes is 14 in 1000 – compared with 10 in 1000 for those who do not have it on either, they say (*Nature Genetics 2009 doi:10.1038/ng.424*).

Lead author, Cancer Research UK scientist, Professor Paul Pharoah (University of Cambridge, UK), said that BRCA1 and BRCA2 mutations do not account for all of the inherited risk of the disease. 'It is likely that

'IT WILL HELP DOCTORS MANAGE WOMEN AT INCREASED RISK'

the remaining risk is due to a combination of several unidentified genes – which individually carry a low to moderate risk. Now we have ticked one off, the hunt is on to find the rest.'

Senior author Dr Simon Gayther (University College London, UK), said: 'There is now a genuine hope that as we find more, we can start to identify the women at greatest risk and this could help doctors to diagnose the disease earlier when treatment has a better chance of being successful.'

Dr Lesley Walker (Cancer Research UK) said the finding could lead to new approaches to treatment or prevention. 'Crucially it will help doctors manage women who are at increased risk,' she said.

Thalidomide 'does not improve survival' in SCLC

Thalidomide combined with chemotherapy does not improve survival in small cell lung cancer (SCLC) but is associated with an increased risk of thrombotic events, UK researchers say.

A double-blind randomised controlled trial involving 724 patients compared thalidomide plus chemotherapy (etoposide and carboplatin) with the chemotherapy plus a placebo. Patients were studied for up to 2 years.

'THE STUDY CLOSES THE DOOR TO USING THALIDOMIDE IN SMALL CELL LUNG CANCER'

Median overall survival was 10.5 months for patients receiving the placebo, and 10.1 months for those on thalidomide. There was no survival difference among patients with limited-stage disease, but in those with extensive disease, survival was worse in the thalidomide group (*J Natl Cancer Inst 2009 101 (15):1049–57*).

Furthermore, thalidomide was associated with an increased risk of thrombotic events, mainly pulmonary embolus and deep vein thrombosis (19% for thalidomide versus 10% for placebo). Quality of life scores were similar in the 2 treatment groups but thalidomide was associated with less insomnia and diarrhoea and more constipation and peripheral neuropathy.

The anti-angiogenic agent has remained in the public eye since its use in pregnant women 50 years ago led to major birth defects in their children. Its use was prohibited but more recently, the drug has shown promise as a treatment for some cancers, including myeloma.

An accompanying editorial (*J Natl Cancer Inst 2009 101 (15):1034–5*) stated that the study 'definitely closes the door to using thalidomide in small cell lung cancer.'

No-go for cetuximab in NSCLC

The European Medicines Agency (EMEA)'s Committee for Medicinal Products for Human Use (CHMP) has adopted a negative opinion on use of cetuximab (Merck Serono's Erbitux) in non-small cell lung cancer (NSCLC). The drug is used to treat metastatic colorectal cancer and squamous cell cancers of the head and neck; CHMP is recommending refusal of an extension of indication to include NSCLC.

Cetuximab plus platinum-based chemotherapy significantly prolonged median overall survival compared with chemotherapy alone (11.3 versus 10.1 months, respectively) in the phase III FLEX trial. It included 1125 patients of all histological NSCLC subtypes, and Merck Serono said that the addition of cetuximab 'was tolerated with manageable side effects.'

CHMP, however, was concerned that benefits were modest in terms of survival times and that the medicine 'did not have a convincing effect' on progression-free survival. Severe side effects were seen in some patients receiving the drug, and the Committee concluded that benefits did not outweigh risks.

The balance of benefits and risks for the use of cetuximab in colorectal or head and neck cancers remains unchanged, CHMP said, and patients currently included in clinical trials with the drug will continue to receive it.

Merck Serono has requested a re-examination of the opinion, stating that the drug is the only targeted compound in clinical development in more than 10 years to increase overall survival in a NSCLC patient population including all histologies. The company said that, following consultation with key stakeholders in the NSCLC treatment community, it will work closely with CHMP 'to unravel the value of Erbitux'.

Zalutumumab: partial hold lifted

The US' Food and Drug Administration has lifted the partial clinical hold on zalutumumab studies being conducted under an US Investigational New Drug Application, Genmab announced.

It means that enrolment of patients can resume in the phase II study in head and neck cancer considered incurable with standard treatment, and the phase I/II front line study of zalutumumab in combination with chemo-radiation.

PODIUM

Relapsed ovarian cancer: no rush to start treatment

Professor Gordon Rustin (Mount Vernon Cancer Centre, Middlesex, UK) presented data from a multi-institutional phase III ovarian cancer trial at the 2009 American Society of Clinical Oncology Annual Meeting. It found that early treatment of recurrent disease based on rising CA125 biomarker levels does not improve overall survival, compared with delaying treatment until symptoms arise. The study could change practice.

What were the results of your study?

The patients in the early treatment arm were treated 4.8 months earlier than those in the delayed treatment arm and, despite this, received their next (third) line of treatment 4.6 months earlier. Earlier treatment did not give them a longer remission. Survival rates in the two arms were identical, but the group on earlier treatment had a worse quality of life. These results mean that there is no benefit from early detection of relapse by routine CA125 measurement.

Also, even if a patient's CA125 levels rise, but she is well, she can now be reassured that she does not have to rush into immediate treatment and can plan her life better.

Were these results expected?

My suspicion early on was that there would probably be a 6 week survival advantage in the early treatment group but a worse quality of life because of having more chemotherapy.

What do the results mean for women with ovarian cancer?

There are huge implications. I have been telling my patients for some months now the results of this trial and advising them not to have routine CA125 measurements. We give them a symptom checklist of the things they should worry about, and if they are at all worried, they should immediately have a CA125 blood test and contact us.

My experience so far is that probably about 80–90% of women opt not to have routine CA125 follow-up.

What has the reaction been to your study from the oncology community?

There have been several. Some people were afraid that healthcare providers might use our data to say that women could no longer have CA125 follow-up, i.e. that they would not pay for it. I was keen to make the point that this trial suggests that women should be offered an informed choice, and my experience is that the great majority decide not to have the CA125 follow-up. But there is reasonable concern among patient groups that they might not be allowed the choice by healthcare providers, and we have got to address this.

Many feel that the result is counter-intuitive because we tend to believe that early treatment is better. Perhaps our paradigm has been wrong…if you have a cancer that relapses locally and which can be surgically resected, earlier treatment might be better, but the situation with ovarian cancer is very different and relapses tend to be disseminated.

Do you expect your findings to be widely taken up?

The Selection Committee at ASCO put this study as the number one plenary abstract, so they must have seen the importance of this study. More generally, people who practise scientific evidence-based medicine are likely to follow these results and alter their practice. Those who practise emotional medicine are going to be a bit torn and will probably need more convincing. Those who practise commercial medicine are going to be upset because the results will hit them in their pockets and they will probably ignore the findings.

It is crucial that we get the message across to patient groups so that patients can make their own decisions. I think practice will change but we have a big educational job on our hands to get the message across.

What research is on-going?

We are trying to establish the proportion of women who will decide they are prepared to opt for no follow-up using CA125, and indeed, whether we should be looking at information packs and telephone follow-up for patients who may not want to come to the clinic.

We also need to look at coping strategies and discover how to educate the patient to make what we consider the right decision. Also – and this is going to be more difficult – are there coping strategies that we can offer once patients' CA125 goes up? My experience is that once somebody knows their CA125 is going up, any subsequent niggle will trigger their fear that the cancer is growing and they will want to start treatment. Most of these women, even if given the option of delaying treatment, do start treatment fairly soon.

The results of this trial mean that I can tell patients that there is definitely no evidence to suggest that earlier treatment helps, so if they are well we can keep waiting. We will have to wait and see whether this innovation will reduce people's anxiety enough for them to choose to delay treatment.

Robert Day-Webb