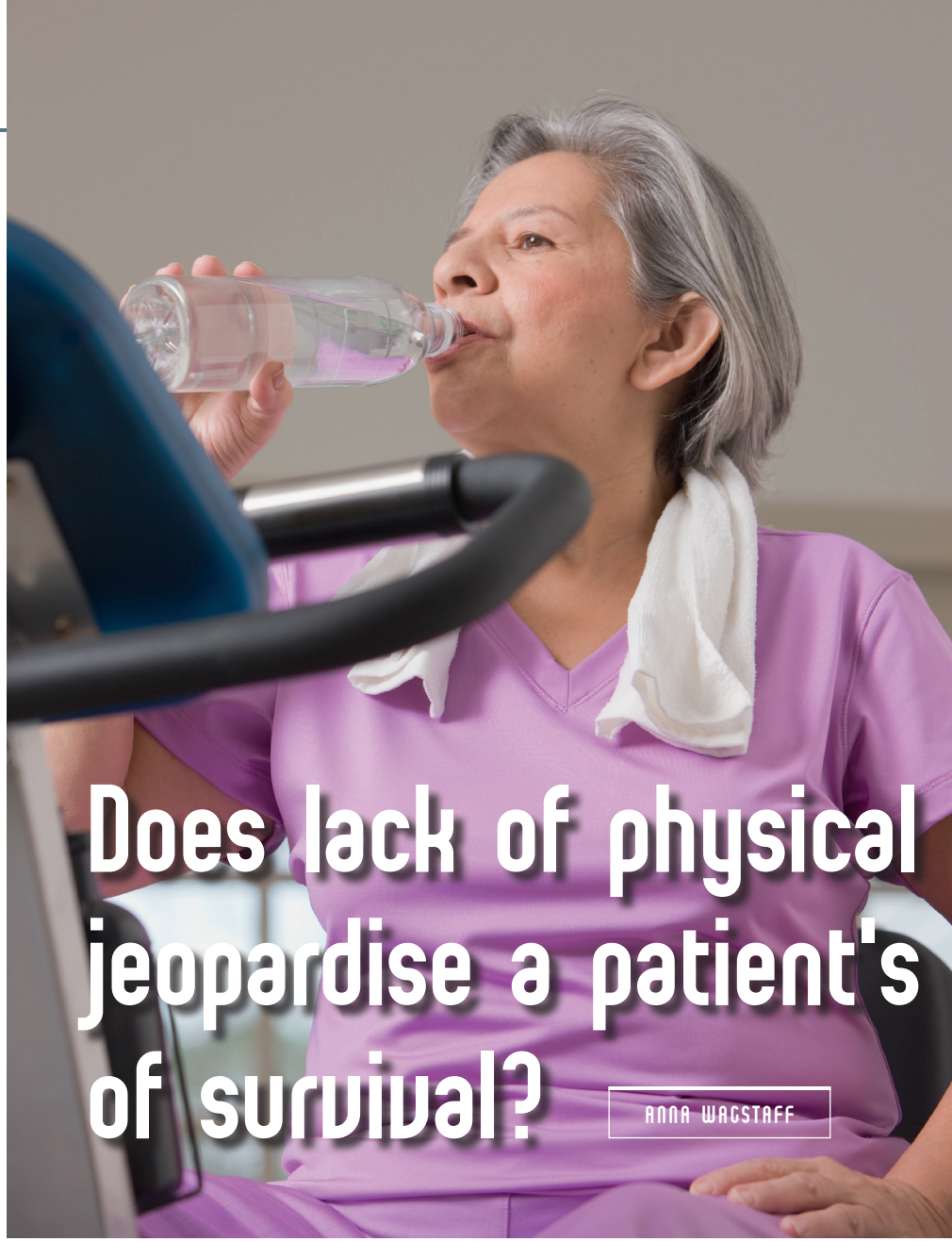

Does lack of physical jeopardise a patient's of survival?

ANNA WAGSTAFF

Exercise reduces the risks of getting some cancers – but what about after diagnosis? What should we be advising our patients?

"Be physically active in everyday life. Limit the time you spend sitting." So says point 4 of the European Code Against Cancer, the 12-point official EU guide to how to lower your risk of getting cancer.

The advice emanates from an impeccable source – the WHO's International Agency for Research on Cancer. It is based in large part on a growing body of evidence showing that a wide range of cancers – but particularly breast and colorectal – are less common in people who are more physically active, keep their weight down and eat a healthy diet.

Adding to this epidemiological evidence is a steady stream of biological studies throwing light on what it is about these healthy behaviours that leads to the lower cancer risk.

As ever, it's not a simple picture. Current evidence indicates that 'energy balance' – the net effect of food (energy intake) and exercise (energy expenditure) – may affect genomic instability, dysregulated growth signalling and cellular energetics, inhibition of apoptosis and of immune surveillance, and angiogenesis. That's five of the ten classic 'hallmarks' of cancer.

But key aspects of the relationship remain unclear. For instance: does physical activity have a direct impact on reducing cancer risk, or does it work mainly through weight loss? How much of the observed correlation between physical exercise and cancer might be explained by the fact that people who exercise more are generally more proactive about their health?

With obesity and more sedentary lifestyles on the rise, the weight of evidence for a cancer link pointing only one way, the proven benefits of exercise on general health, and the lack of associated risks, IARC, the EU and the cancer community are not waiting for more and better evidence: be more active to reduce your cancer risk is the official advice to the general public.

However, when it comes to people who have already been diagnosed with cancer, the question of what to advise – or prescribe – on the basis of current evidence is altogether more controversial.

This January, a report into the role of physical activity and sport in oncology (*Oncol Hematol* 2015, 94:74–86) reviewed the results of eight major studies that looked at how being physically active after having been diagnosed with localised breast cancer impacted on survival. It argued that the data showed "A physical activity higher than

exercise chances

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8–9 metabolic equivalent task (MET)-hour per week was associated with a 50% reduction in mortality from both cancer and all causes," and that this translated into a benefit of 4–6% in terms of 5-year and 10-year survival.

As lead author Thierry Bouillet, an oncologist at Avicenne Hospital in Paris, points out, this is "the same benefit as chemotherapy".

While these are observational studies, Bouillet believes they build a credible picture, because they are large – the smallest with just under 1,000 patients, the largest almost 5,000 – and because they account for key confounders such as weight, drinking and smoking habits, and give fairly consistent results.

He also points to stronger evidence from a number of randomised controlled studies on the effect of physical activity in helping patients feel and function better. Bouillet mentions, in particular, the impact on reducing fatigue, which he says is the number one problem reported by breast cancer patients following treatment with chemotherapy, radiotherapy or surgery, and cannot be improved, for instance, by sleep or rest.

Other studies have shown an association between physical activity after breast cancer diagnosis and better mental health, better social and physical function, lower weight, and improved self-esteem. While these are all important in terms of quality of life, as Bouillet points out, they may also feed in to better adherence with therapy, which will have a knock on effect in improving survival.

Bouillet is in no way advocating that physical activity should be prescribed as an alternative to chemotherapy. He does believe, however, that its impact on the course of the disease means that there is now an overwhelming case for prescribing it in addition to chemotherapy for women with early breast cancer.

A 'no' from St Gallen

But when a panel of experts was asked, this March, whether the adjuvant therapy clinical guidelines for treating this group of patients should be updated to include physical activity, the answer was negative.

This was the consensus panel of the St Gallen conference, which every two years meets to deliberate on new evidence and update clinical guidelines on the primary treatment of early breast cancer. And when they came to look at the evidence for an impact of physi-

This translated into a benefit of 4–6% in terms of 5-year and 10-year survival

Exercise as therapy. This karate class uses techniques developed by the French Federation of Sport and Cancer, which are adapted to fit the therapeutic needs, physical abilities and medical risk of patients

CAMI

cal activity on cancer outcomes, they were simply not convinced, although the panel did endorse prescribing both physical activity and weight loss for their general health benefits.

A key voice questioning the quality of evidence for a survival impact was Pam Goodwin, a medical oncologist at the University of Toronto's Mount Sinai Hospital, who has spent much of her career researching lifestyle factors associated with breast cancer.

She argues that the evidence for an impact of greater physical activity on cancer outcomes in early breast cancer is simply not strong enough to tell patients their breast cancer outcomes will be improved if they become more active or lose weight. "The St Gallen adjuvant therapy guidelines focus on breast cancer specific survival and reduction in risk of recurrence. It wasn't that I or anybody else was opposed to having breast cancer patients who are interested in being physically active be active – there's no problem with that. The issue is that we don't have the evidence to tell them that it will improve their breast cancer outcomes."

Goodwin points out that large series of observational studies don't have a particularly good track record, "It's like the old story of HRT and breast cancer risk. For years the studies said the benefits outweighed the risk, but when the randomised studies were done, we found that the breast cancer risk was increased with the commonly used combination therapy, and a lot of the added benefits we thought existed didn't."

Observational studies, she argues are wide open to bias and confounding, "and in these types of studies, the obvious bias to be concerned about is a healthy person bias."

"If you take a thousand breast cancer patients, and show that those who are more physically active have better outcomes, better overall mortality, and some evidence of lower breast cancer mortality, what we don't know is whether those women in general are healthier. The way that could impact the results is that healthier women could be in general more compliant with screening programmes, more likely to have their breast cancers diagnosed at an earlier stage, and more compliant with their breast cancer treatment. And you can try to adjust for all of that, but the reality is that you can't fully adjust, in the absence of data from randomised trials."

Goodwin raises the possibility that the causal link may also work the other way around, that women who are generally less healthy may get more aggressive cancers, and that the biology of that cancer may be "built in" at the time of diagnosis and therefore not amenable to change by increased physical activity (or weight loss) post diagnosis.

It was because of these uncertainties that the panel took the decision it did. "We felt we should apply the same standards in evaluating evidence on physical activity and obesity as we use for drug treatments," says Goodwin. "In other words we want clear data relating to efficacy before we say to breast cancer patients: 'If you do this, your outcomes will be better.'"

If there was no way to generate that data, she adds, then maybe the panel would have taken a different approach. However, randomised controlled trials are ongoing or about to start looking at the impact of physical activity and weight loss on cancer prognosis. CHALLENGE, led by the National

"We don't have the evidence to tell them that it will improve their breast cancer outcomes"

Cancer Institute of Canada, is a randomised trial generating evidence on the impact of exercise on recurrence in colon cancer, while Jennifer Ligibel's team at the Dana Farber in Boston is set to launch a randomised controlled trial to get data on the impact of weight loss on breast cancer outcomes. Like all survival studies, they will take time, but the answers they give should be reliable.

Bouillet finds this reasoning highly frustrating. A founding member of CAMI, the French National Federation of Sport and Cancer (sportetcancer.com), and himself a karate blackbelt, he's spent 15 years building evidence, changing attitudes and developing practice around the role of physical activity and sport in cancer. He doesn't see the need to wait a further 10 years.

"We started in 1998. In the beginning nobody believed in us. In those days, the main thing for physicians was to say: you have cancer, you must rest. No movement, no sports, nothing. It took a long time to change people's minds."

Today the CAMI federation has almost 60 partner institutions across France that run courses in karate, modern dance, yoga and Täi chi, specially adapted for people with different types of chronic medical conditions. Most courses are run at local gyms and leisure centres, but Bouillet says that hospitals are increasingly getting involved. The Institut Gustave Roussy, for instance, is a CAMI affiliate, and hosts dance and karate classes every Monday and Thursday.

Each course, explains Bouillet, is designed to give the right type of exercise as well as the right intensity: "Enough to break sweat, regularly, three times a week, for six months is needed for biological and clinical modification," he says.

Risk assessment is done by the patient's doctor, who must sign a form for them to participate, and the courses are led by qualified instructors with a one-year university diploma in Sport and Cancer.

French health policy

The CAMI project received a major boost in April, when the principle of prescribing physical activity adapted to the patient's "pathology, physical abilities and medical risk" was introduced as an amendment into a new piece of health legislation – Loi de la Santé – as it passed through the French National Assembly. The amendment sets the framework for such a service, spelling out the governance of the organisations and instructors responsible for delivering the courses, and the responsibilities for training physicians in prescribing "adequate physical activity". It paves the way for this sort of exercise to be reimbursed as a medical treatment through health insurance.

A summary statement published in association with the amendment refers specifically to breast cancer treatment, spelling out the benefit of physical activity for counteracting fatigue, but more controversially mentioning its impact in reducing recurrences and increasing survival chances by more than 50% – a figure that also appears on the CAMI website.

Oreste Gentilini, a breast surgeon at the European Institute of Oncology in Milan, is not yet convinced about the numbers on survival, but believes Bouillet has certainly got one thing right: physical activity can do a lot of good for people who have been treated for breast cancer, and the medical profession is letting its patients down by not taking time to explain its benefits. He argues for a culture change.

"For too long we've been forgetting the importance of having a healthy lifestyle. In order to convince our patients, we first have to be convinced ourselves. This is not easy because physicians tend to highlight research on what is achieved by direct medical interventions, either surgery or drugs or whatever. But the data available at the moment are solid enough, and basically they all go in the same direction, supporting lifestyle as a preventive and also therapeutic measure. So we should take time to explain to patients the results."

He points out that after the shock of being diagnosed and treated for early breast cancer, people often look for advice about what they can do for themselves to improve their survival chances. Many doctors do talk about the importance of taking time to be physically active and exercise on a regular basis, says Gentilini, but they often fail to clearly explain why, and how much patients could benefit.

Gentilini is himself involved in research on the impact of physical activity on patients' quality of life, and acknowledges that it is difficult to get

hard evidence on the impact on recurrence and survival. He is currently recruiting to a randomised controlled trial looking at the benefits of a moderate increase in exercise for women with a sedentary lifestyle who have had breast cancer, but this will look at the impact on quality of life, and some biological parameters, not at survival.

He argues, however, that on the basis of the current evidence, doctors should be advising their patients of the survival benefit conferred by physical exercise. "I'm not sure if it provides a 50% or 40% or 30% reduction, but all the studies which were conducted showed a reduction in mortality or risk of recurrence, and we cannot ignore this any more."

Pamela Goodwin, in contrast, has no doubt that the guidelines consensus panel was right to insist on better evidence before advising patients that physical activity or weight loss confers any survival benefit. She points to research being undertaken at the Fred Hutchinson, led by Anne McTiernan, about diet, physical activity and obesity, which indicates that all three impact on physiologic mediators of the link between lifestyle and cancer – such as oestrogens, insulin and inflammatory markers – but these impacts are greatest with weight loss and diet, and occur to a much lesser extent with physical activity alone.

A situation of 'equipoise'

"We're in a situation of equipoise in relation to breast cancer outcomes," says Goodwin. "We have enough evidence to start a trial. We're all hoping that the observational evidence will be confirmed. But we have to be careful with our patients. I talk to all my patients about this, and recommend lifestyle change. We have a wellness programme at our centre, where we introduce women to physical activity, we give them individualised programmes, individualised diets after a diet assessment, and weight loss goals if they are overweight. And there's a group who really enjoy that."

But as she points out, there are also many women who do not enjoy it. "Part of it is that they don't want to feel guilty that they contributed to their cancer, or the recurrence of their cancer if they do not adopt a healthier lifestyle. But part of it is that these are women who have not been very active and many of them are overweight. And some resist the lifestyle change. In the absence of evidence that it will improve their outcomes, all I can say to them is that we are studying this, we hope future research will show it can improve survival, but we don't know for sure."

So what about the French National Cancer Institute INCa? Do they back the St Gallen position, and if so, what do they think of the amendment to the Loi de la Santé?

Julie Gaillot, INCa's lead on tertiary prevention, is clear that there is still uncertainty about the impact on survival: "We can say that even though observational studies seem to show an effect, for the moment it has not been confirmed through randomised controlled trials."

As for the amendment to the Loi de la Santé, Gaillot explains that INCa was not consulted. She agrees that, on the basis of current knowledge, it would be wrong to suggest that physical activity can lead to a 50% reduction in mortality risk. However, she expects that this wording is likely to change when the proposed legislation is scrutinised by the upper house, the French Senate, later this year.

On a broader note, Gaillot certainly backs the general principle that doctors should be encouraging patients to be more active, and she agrees that a change of mentality is needed. "It's hard for doctors to introduce physical activity, because they are not trained and educated about the benefits of exercise for people who are ill, whether it's cancer or other chronic illnesses, or in the general population."

Widespread coverage in the mass media, she says, is sparking interest among patients and health professionals, many of whom are looking for good advice. INCa has the responsibility to provide that advice, which it will do, she says, but only based on validated evidence.

For Gaillot, this means primarily the evidence from randomised controlled trials regarding benefits on fatigue, quality of life, body composition and fitness – and not just about participation in sports but more generally adopting a less sedentary lifestyle. These recommendations will need to be specific about the type, the amount and the intensity of exercise needed to achieve specific benefits, she says.

And they will not endorse any specific benefit on survival: "We would first need more solid evidence," she confirms. ■

"For too long we've been forgetting the importance of having a healthy lifestyle"