therapy change, meaning that other approaches should be preferred as first-line therapy.

Numerous studies have analysed the clinical activity of extracorporeal photochemotherapy in patients with cutaneous T-cell lymphoma, although the majority are retrospective or single-centre and include relatively small patient cohorts. The proportions of patients achieving a response range between 33% and more than 90%, with mean values of 63% with complete responses in about 20% of cases.7

Two randomised studies8,9 have documented the clinical efficacy of new drugs brentuximab vedotin and mogamulizumab in pretreated patients with cutaneous T-cell lymphoma. In the ALCANZA trial, a randomised phase 3 trial comparing brentuximab vedotin versus methotrexate or bexarotene in CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma, patients with high blood Sézary cell counts were not included; however, the clinical activity of brentuximab vedotin has been reported in patients with Sézary syndrome in previous phase 2 studies. In the MAVORIC trial, a phase 3 randomised trial comparing the anti-CCR4 antibody mogamulizumab with vorinostat, the proportion of patients with a response in the blood was 68% and global responses in Sézary syndrome occurred in 30 (37%) of 81 patients. The median duration of response in the blood was 25.5 months (IQR 15.9–not estimable) and in the skin 20.6 months (11.2–not estimable), with 36 (20%) of 184 patients developing serious adverse events considered treatment related.

The results reported by Bagot and colleagues1 in this phase 1 study of IPH4102 are encouraging. However, they need to be confirmed in phase 2 and 3 trials, together with the identification of parameters associated with a better clinical activity that could drive patient selection. Future studies could also attempt to ascertain the position of this treatment in the treatment of patients with Sézary syndrome. At the moment, we could speculate that adopt this targeted approach in patients refractory to, or who have relapsed after, extracorporeal photochemotherapy, but also in association with it or even before, particularly in patients with a large tumour burden in the peripheral blood who are less responsive to standard therapies. Moreover, similarly to mogamulizumab, IPH4102 could also be considered as a bridge to allo transplant in young candidate patients.

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Of microbes and women: BRCA1, vaginal microbiota, and ovarian cancer

The human body is home to several niche-specific microbial communities (termed microbiota), which, through host–microbe networking, are thought to have an integral role in human physiology. Many observational studies have shown differences in terms of the composition of bacterial microbiota (and much less frequently of viral and fungal microbiota) between healthy people and those presenting with various conditions.

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conditions. Such differences are postulated to suggest that dysregulation of microbiota–host interactions (termed dysbiosis) is a putative disease mechanism in a myriad of conditions. Although most microbiome-wide studies so far, including those done in oncology, have been cross-sectional, which precludes the deduction of causal inferences and means that the findings are prone to bias and confounding, the human microbiota could nevertheless be a promising target for various aspects of cancer prevention and treatment.

In The Lancet Oncology, Nuno Nené and colleagues report the findings of a case-control study in which they used 16S rRNA gene sequencing to characterise the cervicovaginal microbiota, which was sampled in women with epithelial ovarian cancer before treatment (the ovarian cancer set) and women with the BRCA1 mutation in whom ovarian cancer had not yet developed (the BRCA set). Both sets were matched with a mixture of healthy controls and controls with benign gynaecological conditions. Among the 85 participants younger than 50 years of age in the ovarian cancer set (69 [81%] of whom were premenopausal), cases with ovarian cancer were more likely to present with a community type O cervicovaginal microbiota (ie, one in which lactobacilli accounted for less than 50% of the total bacteria present) than were age-matched controls, after adjustment for a set of key covariables (adjusted odds ratio 2.80 [95% CI 1.17–6.94]).

Nené and colleagues’ decision to dichotomise cervicovaginal microbiota status with a 0.5 rank abundance cutoff for lactobacilli (ie, <50% lactobacilli vs ≥50% lactobacilli) is unconventional but pragmatic. In most populations, the vaginal microbiota in women of reproductive-age is largely dominated by niche-specific lactobacilli, and deviation from this state is associated with a range of adverse reproductive health outcomes. However, the vagina is also a highly dynamic ecosystem, and by assessing the microbiota on only one occasion, there is a risk of misclassification bias in the authors’ findings.

Irrespective of these and other methodological issues, such as the cross-sectional design of the study, the highly novel findings presented by Nené and colleagues beg the question as to how the vaginal microbiota relate to ovarian neoplasia. Vaginal microbiota status could be a proxy variable reflecting the plasticity of the microbiota to extrinsic factors that are potentially involved in ovarian carcinogenesis, albeit through non-microbial pathways—for example, smoking is assumed to negatively affect lactobacillus dominance, whereas by contrast oestrogen-based hormonal contraception and hormone replacement therapy are thought to enhance it. More direct, mechanistic associations should also be considered. Banerjee and colleagues have described a fairly consistent ovarian microbiota signature that is associated with ovarian cancer. Although these associations could also be a consequence of reverse causation (ie, cancer leading to microbiota alterations in the tumour environment), and the origins of the ovarian microbiota remain elusive, some researchers have suggested that the vaginal microbiota acts as a so-called microbial seed bank for the upper genital tract. Biofilm-associated vaginal dysbiosis can ascend to the endometrial cavity and fallopian tubes, and such a process could hypothetically have a role in the complex, extra-ovarian origins of ovarian epithelial cancers. Notably, pelvic inflammatory disease, the key clinical example of ascending female genital tract infection, is cautiously thought to be a potential risk factor in ovarian cancer.

Less obvious mechanisms could also be involved in the relationship between cervicovaginal microbiota and ovarian cancer. Of particular interest in this respect was Nené and colleagues’ finding that BRCA1 mutation carriers aged younger than 50 years were also more likely to have community type O (ie, lactobacilli-depleted) cervicovaginal microbiota relative to controls wild type for BRCA1 (odds ratio 2.79 [95% CI 1.25-6.68] after adjustment for pregnancy [ever]). Assembly of tissue-associated microbiota is co-driven by the human genome, which possibly explains why loss-of-function mutations in tumour genes have been associated with composition of the gut microbiota. Although only 10–15% of women with incident ovarian cancers have a BRCA1 mutation, the associations between end-organ cancer, BRCA1 mutation, and dysbiosis of anatomically distant but possibly related microbiota highlight the complexities of ovarian carcinogenesis and disentangling the roles of known risk factors in the process.

Accordingly, rather than making a case for probiotic treatment, as suggested by the authors, these findings
Cancer and night shift work: what we still do not know and why

The International Agency for Research on Cancer (IARC) have categorised night shift work as probably carcinogenic to humans. This news is potentially concerning—but what does this assessment mean and, perhaps more importantly, what does it not mean?

Like all such IARC categorisations, it tells us nothing at all about the actual risks to night shift workers. The classifications weigh up the strength of evidence that there could be a potential risk under certain circumstances. Whether in practice there is an actual risk, and if so, how big that risk is, is something that the IARC does not consider in deciding the category. This distinction is made clear in the Q&A document that they released.

Their conclusion is that night shift work probably can increase the risk of cancer in humans under certain circumstances—that is exactly what they mean by “probably carcinogenic to humans”. But they do not state which circumstances or how much increased risk. And, because they say “probably”, there remains a possibility that shift work cannot affect human cancer risk at all.

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I declare no competing interests.
