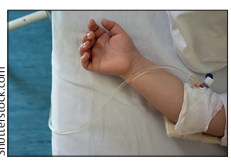
Global burden of childhood cancer: growing, but controllable



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There are many facets to the burden of childhood and adolescent cancer. Unsurprisingly, these are best documented in the predominantly high-income countries that have high-quality population-based cancer registries and death registration systems. In those countries, cancer is largely a disease of older adults, with well under 2% of cases diagnosed in the first 20 years of life (data from the Cancer Today database). More than half a century of progress in therapy and supportive care for children with cancer has resulted in impressive gains in survival and corresponding reductions in population mortality rates in high-income countries. However, this success has come at the price of increased long-term morbidity and mortality among survivors compared with the general population, which must also be counted as part of the cancer burden.[1,2] In their Article in *The Lancet Oncology*, Lisa Force and colleagues[3] estimate, for the first time, the global burden of childhood cancer in disability-adjusted life-years (DALYs), taking into account loss of healthy life-years to ill health and disability in addition to death.

The overwhelming majority of cases of cancer in children and adolescents (those aged younger than 20 years) occur in low-income and middle-income countries, which thus bear a correspondingly large part of the global cancer burden for this age group.[4,5] A notable feature of the study by Force and colleagues is its stark demonstration of the absolute and relative scale of the burden in lower-resource countries and how it contrasts with that in high-income countries. High and high-middle Socio-demographic Index (SDI) countries account for 35% of global childhood and adolescent cancer incidence, but only 18% of DALYs, whereas low-middle and low SDI countries, with 38% of global incidence, account for 60% of DALYs. Worldwide, years of life lost represent 97·3% (95% uncertainty interval 97·3–97·3) of DALYs and years lived with disability only 2·7% (2·7–2·7), but the contribution of years lived with disability to total DALYs ranges from almost 9% (9–9) in high and high-middle SDI countries to less than 1% (1–1) in low-middle and low SDI countries. Force and colleagues note that their estimates probably understate the global burden of years lived with disability, and therefore of DALYs, because consideration of disability was limited to the first decade after cancer diagnosis rather than the entire remainder of the life course.

How can the global burden of childhood and adolescent cancer be expected to evolve in the future, and what can be done to mitigate or even reduce it? As the population at risk increases—mainly in low-income to middle-income countries—the number of incident cases will also increase, and the total and proportional burden of childhood and adolescent cancer on lower-resource countries will become even larger. Childhood and adolescent cancer is much less amenable to prevention than many major cancers of adults, for which risk factors can be reduced or even eliminated. Immunisation against hepatitis B where it is endemic has resulted in a reduced incidence of liver cancer,[6] but most of the effect will be seen in adults, and liver cancer accounts for less than 2% of the global burden of childhood and adolescent cancer. Avoiding excessive exposure to ultraviolet radiation at young ages will lessen the risk of melanoma, but again principally among adults. In sub-Saharan Africa, the waning of the HIV epidemic should lead to a reduction in Kaposi sarcoma and progress against malaria could reduce the burden of Burkitt's lymphoma. The history of population screening for childhood cancer is not encouraging. The only feasible target was neuroblastoma, but screening led to overdiagnosis of cases that would have regressed without symptoms and had no effect on mortality from the more aggressive forms of this cancer.[7]

Earlier diagnosis through greater public and clinical awareness could bring a short-term rise in global burden for children and adolescents because fewer cancers with onset before the age of 20 years would actually be diagnosed after that age; this change would particularly affect cancers that can have a relatively protracted natural history, such as Hodgkin lymphoma and thyroid carcinoma. Overall, however, early diagnosis can bring substantial reductions in mortality and long-term morbidity. Although gains from early diagnosis should be greatest in lower-resource countries, where too many cases are diagnosed at a late stage, they should be felt even in affluent countries, notably for people with low-grade brain tumours, survivors of which bear a considerable burden of disability.[8] For the benefits of early diagnosis to be fully realised worldwide,

it must be accompanied by improved diagnostic and treatment facilities with universal access. International collaboration will be an essential component of the necessary capacity building.[9] It is to be hoped that the present study will help to stimulate the necessary improvements, and future iterations can monitor their success.

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I declare no competing interests. The author alone is responsible for the views expressed in this Comment and they do not necessarily represent the decisions, policy, or views of Public Health England.

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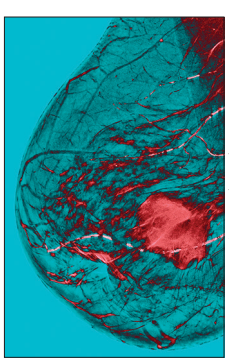
Overcoming endocrine resistance in neoadjuvant endocrine therapy for early breast cancer

Endocrine therapy is the mainstay of treatment for oestrogen receptor-positive breast cancer, now classified as either the luminal A (HER2-negative with low levels of Ki67) or luminal B (HER2 positive or negative, with high levels of Ki67) phenotype. Historically, endocrine therapy has included the approach of targeting the oestrogen receptor itself, either by means of selective oestrogen receptor modulators such as tamoxifen, or fulvestrant, a selective oestrogen receptor degrader. Another mode of action is the inhibition of oestrogen production so that no ligand is available to activate the receptor. This is the mode of action of aromatase inhibitors, which block the aromatase enzyme and lower oestrogen levels in postmenopausal women; whereas in premenopausal women, luteinising hormone-releasing hormone agonists reduce oestrogen production in the ovaries by interacting via the regulatory axis from the pituitary gland to the ovary. Since the 1990s, data have suggested that aromatase inhibitors might be the optimal neoadjuvant endocrine therapy treatment approach in postmenopausal women with breast cancer, resulting in better overall responses, improved pathological complete responses, and increased breast conservation at surgery.[1] More empirically, a 3-month period for neoadjuvant endocrine therapy was introduced as the standard of care in postmenopausal women with breast cancer in the mid-1990s. However, compared with neoadjuvant chemotherapy, neoadjuvant endocrine therapy has always yielded inferior results in terms of pathological complete responses.[2] Once introduced in the metastatic breast cancer setting, combinations of endocrine therapy plus mTOR inhibitors or CDK4/6 inhibitors instantly changed the standard treatment approach. However, resistance and disease progression while on treatment have occurred in both the adjuvant and metastatic settings.[3]

Apart from oestrogen expression, receptor levels, and to some extent a decrease in Ki67 levels, no biomarker has been identified as a prognostic marker for the benefit of neoadjuvant endocrine therapy. The phosphatidylinositol 3-kinase (PI3K) pathway is frequently altered in oestrogen receptor-positive breast cancer and has been implicated in resistance to endocrine therapies.[4] Furthermore, *PIK3CA*, which encodes the PI3K p110α isoform, is mutated in approximately 40% of oestrogen receptor-positive breast cancers.[5] Oestrogen-independent breast cancer cell growth can be inhibited by adding PI3K inhibitors to anti-oestrogens.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