Understanding Breast Cancer Survival with Epidemiology

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There is convincing evidence to suggest that lifestyle factors are important in both the development and progression of breast cancer, and a significant number of cases may be prevented if diet, activity and weight modifications were adopted by appropriate groups of individuals [1]. The American Institute for Cancer Research [2] estimates that approximately 38% of breast cancers may be preventable, yet concurrently 49,564 and 397 cases of female and male breast cancers respectively were reported in 2010 and almost 11,600 patients succumbed to the disease in the UK that same year [3]. Considerable efforts to understand these statistics and to develop Public Health measures targeting decreasing incidence and mortality rates are on-going, yet recent evidence suggests that there is still much work to be done [4].

The role of epidemiology in understanding how diet and lifestyle affect breast cancer outcomes

In vitro and *in vivo* studies have been key to our understanding of cancer pathology and prognosis. Controlled laboratory investigations clarify how cancer-causing substances (for example: tar, benzene, arsenic and nitrosamines) cause DNA damage and subsequently affect cellular behaviour. Molecular approaches such as those concerned with genome wide analysis, epigenetic, transcriptomic and proteomic changes have started to explain some of these discrepancies, but the role of environment remains a particularly complex area of research. Prospective observational studies of heterogeneous populations in free-living settings have shown that biological adaptations observed in lab-based studies explain only a fraction of cases (for example up to 30% of lung cancer; [5]). Where effects are convincing (and large), the importance of human risk assessment is clear; but the path to discovery of cause and effect where effect sizes are smaller, and perhaps less consistent, is challenging.

Utopia for risk factor epidemiology in breast cancer research would be formulation of prevention and management strategies integrating the best available evidence and linked to measureable health outcome improvements. Patients are however variably exposed (and reactive) to many diverse factors prior to and following a diagnosis of breast cancer. Determining their individual and collective influences on disease-related risk constitutes "a much duller scalpel" [6] than consideration of results obtained from randomised controlled trials. We must acknowledge however that biomedical research is unlikely to address the challenges of either genetic or biological susceptibility to cancer, unless careful consideration of socio-demographic and behavioural factors (among others) is made [7].

Estimates of the population risk of developing cancer must be considered in the context of diverse biological and environmental information. It is clear that exposure to environmental factors must precede the disease outcome. Therefore, the challenge for research teams aiming to elucidate the effects of exposures – both singly or combined (in the so-called 'eposome') – is how best to control for errors including (but not limited to) incomparable diagnostic methods, mis-reporting errors (a particularly relevant issue when quantifying dietary intake estimates and reports of lifestyle habits), biological plausibility, specificity, and consistency. Epidemiology is thought to hold the key to formulation of dietary and lifestyle recommendations, yet interpretation of our work – by all that use it – requires rigour.

It is acknowledged that exposure to risk factors does not remain static: most, if not all, vary within the general population. Action on Smoking and

Figure 1: A complex picture of breast cancer patient diet and lifestyle is collected in the DietCompLyf study. Pink boxes show the information and samples collected by the Study Centres, the blue boxes show information reported by the patients to the coordinating centre.
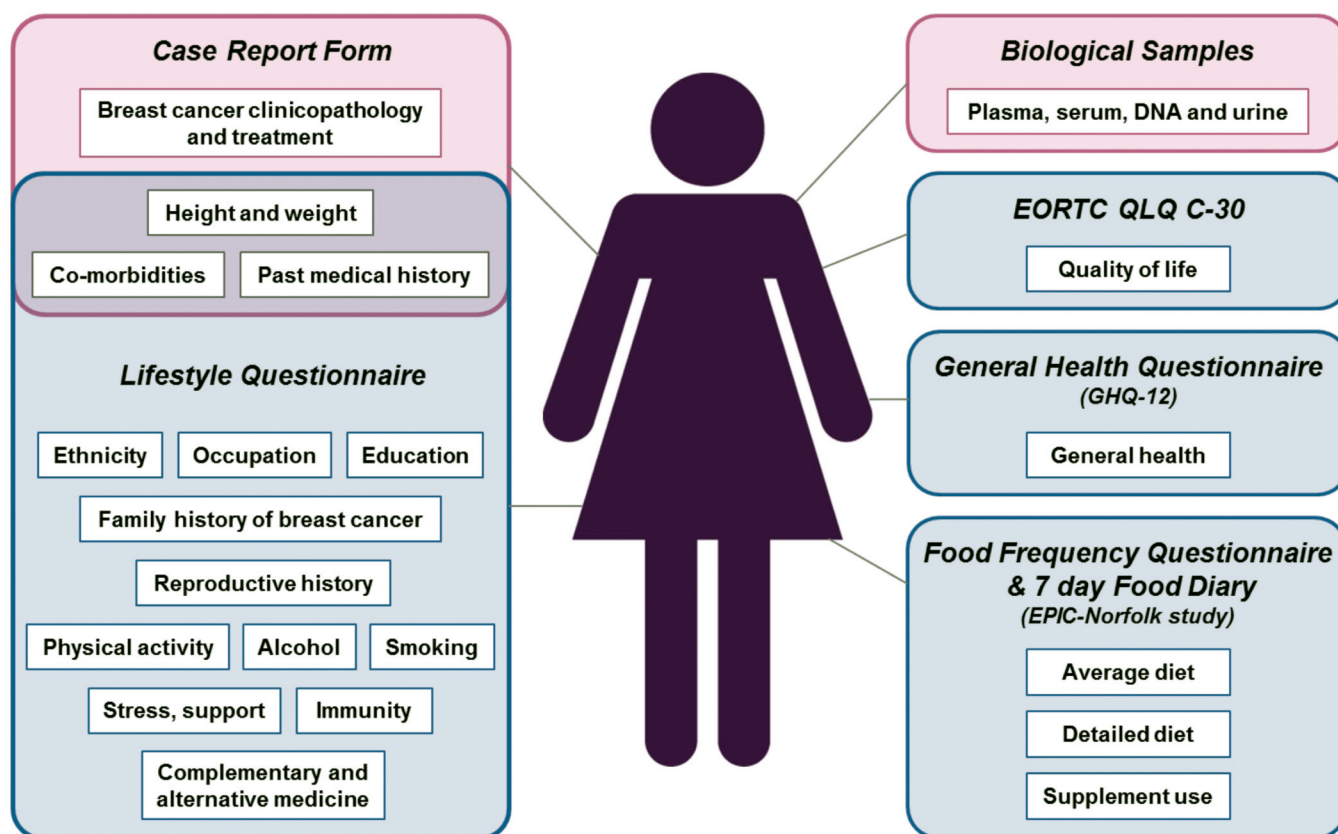
Health [8], for example, estimates that within the UK population, 22% of adult men, 19% of adult women and 32% of those aged 25-35 years smoke. Those in lower social classes smoke more, and regional differences in smoking prevalence are also apparent and relevant. Whether an individual who drinks/smokes infrequently would classify themselves as a drinker/ smoker is subjective and highly variable within and between populations, and from one day to the next. These statistics serve merely to highlight the complexity of factors which scientists must consider in the development of data capture and presentation methods, in quantification and interpretation of biological and lifestyle factors. In essence, to ensure precise and reliable data is captured, enabling confidence in cause and effect associations identified, scientists must "...ensure that they conduct their work with honesty and integrity; to ensure that methods and results are reported in an accurate, orderly, timely and open fashion..." [9].

The World Cancer Research Fund [1] and AICR [2] convene an independent panel of world-renowned experts to consider research evidence on modifiable lifestyle factors including food, nutrition, physical activity and body composition and their relevance to both cancer prevention and disease progression. Where research evidence is convincing, the effects of specific factors on the risk of breast cancer development and recurrence is summarised into a series of recommendations, enabling consistent delivery of sound and substantiated advice by professionally governed health care workers. As part of the Continuous Update Project (CUP), newly published research evidence is reviewed and guidance is updated as necessary [1].

Using epidemiology to inform public health strategies

Health promotion campaigns have successfully been used to target changes in diet and lifestyles, where there is a strong evidence-base to rationalise the need for change. For example: smoking cessation and reduced risk of lung cancer [10], folic acid supplementation and the prevention of neural tube defects [11]. Ajzen and Madden [12] theorise that intentions are 'plans of action in pursuit of behavioural goals' and that compliance may be motivated by the strength of the evidence outlining the benefit of changes.

The evidence base outlining how diet and lifestyle choices may influence breast cancer survival statistics is not yet conclusive. The latest WCRF/AICR Report (2007) gives no specific dietary guidelines at all for cancer survivors beyond "... measures that control body weight may help prevent recurrence, at least of breast cancer" and yet patients want to know what they can eat and what they can do to improve their long-term outcomes. Government policies are clearly needed to facilitate this. AICR/ WCRF (2007) quantify that for each 5kg of weight gained, the risk of developing post-menopausal breast cancer elevates by 5% and risks associated with overweight are

not limited to cancer. *The Healthy Lives, Healthy People* White Paper [13] suggested that an obese woman (BMI ≥30 kg/m²) is almost 13 times more likely to develop diabetes, more than four times more likely to develop high blood pressure and more than three times more likely to have a heart attack than a non-obese woman (BMI <30 kg/m²). Worryingly, data published by the Health and Social Care Information Centre (2013) highlighted that 65% of UK adults were classified as overweight or obese (BMI >25 kg/m²) and only 34% of a normal weight in 2011. If the results from the Government 'Our health, your care, your say' report [14] are representative, patients want to modify their behaviour to prevent the recurrence of cancer and increase their overall health to and to avoid co-diagnosis with other non-communicable diseases (e.g., type 2 diabetes, hypertension), but there is a long way to go before this will be achieved.

We must acknowledge that neither a cancer cell nor the environment in which it is located is a static entity. Drugs used in cancer treatments, the hormonal status of the patients, their diets and nutrition are features which could change the outcomes following a breast cancer diagnosis [15]. Ioannidis [4] highlights an apparent inability for promising results observed in randomised controlled trials to be translated into large scale, population studies and acknowledges that a "quick fix" answer cannot be expected. Randomised clinical trials are prohibitively slow and expensive for the investigation risk factors for cancer, and 'controlled' environments are not realistic for the investigation of long-term outcomes. We must therefore rely on the careful design of case control or cohort studies of large populations. Such projects must also rely on existing evidence of influencing factors, both to ensure collection of relevant information, and to enable appropriate statistical analysis of the effect sizes.

Recruiting a fully representative sample of a complete patient group is not without difficulty, however, and socio-economic, ethnic and cultural variability may affect the utility of results obtained. Confounding biases and measurement errors must be carefully considered when interpreting results from epidemiological studies and biological plausibility must be the cornerstone.

DietCompLyf, an observational study of diet, lifestyle and breast cancer outcome, considered the issues outlined above within its design. The heterogeneity of breast cancer diagnoses alongside the variable influences of patient demographics, clinical decision making, molecular and phenotypic features of the cancer are being considered in a cohort of 3,157 UK women with primary invasive (non-metastatic) breast cancer [16]. Patients were recruited onto the study 12 months (±3 months) post-diagnosis and are (or have been) being actively followed up for 5-years, enabling a plethora of data to be captured and quality control checked prior to exploration of whether diet and lifestyle modifications can influence long-term survival rates for breast cancer patients. 'Diet' is being evaluated comprehensively, using patterns of consumption as well as estimation of individual nutrient intakes calculated from records of food only and from 'food and dietary supplement' use. DietCompLyf is one of the largest studies of lifestyle behaviours and breast cancer survival worldwide [17], and the only such study in the UK. While our cohort does not perhaps contain the 100,000 individuals or 50 years of follow up desired by Ioannidis (2013), the integrity of this — like several other — research group is to utilise epidemiological methods carefully, aiming to advance understanding through observation and exploration of our patients' experiences enabling translation of knowledge into influential recommendations for patients. ●

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