Breast Cancer 100 Years On – What We Have Learnt!

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It is exactly 100 years since George Thomas Beatson, son of the Surgeon-General of the Indian Army, discovered that the natural history of breast cancer was influenced by ovarian function. On 15th June 1895, he removed the ovaries of a 33-year-old woman with post-mastectomy recurrence of disease on her chest wall, following which it completely remitted. The thoughts leading to this unique surgical experiment had been developed many years previously when Beatson was physician to the owner of an estate in the West of Scotland. Observing lambs in an adjoining sheep farm he developed an interest in lactation which led him to recognise that prior to lactation the breast tissue was intensely proliferated, an appearance which almost appeared cancerous. Learning that in Australia cows were castrated immediately following calving to maintain lactation indefinitely, he postulated that the removal of the ovaries might result in a similar 'fatty degeneration' of malignant tissue as was seen in the lactating breast. His theory was wrong; but his experiment a success[1]. A further 28 years were to elapse before the discovery that the ovaries secreted oestradiol provided a rational explanation for this effect[2].

Recognition that the effect of ovariectomy on advanced cancer of the breast was due to reduction of oestrogenic hormones, and that this was applicable only to pre-menopausal women[3], led to the development of other methods of achieving oestrogen deprivation in post-menopausal women. These included the administration of androgens, synthetic oestrogens, progestogens and corticosteroids, and the ablation of the adrenal and pituitary glands[4]. In 1966 these procedures were superceded by the discovery of the anti-oestrogen tamoxifen which is now the endocrine treatment of choice for advanced disease[5]. During these early years there were sporadic reports of ovarian ablation by surgery or radiation as a 'prophylaxis' against recurrence in women with early operable breast cancer, but it was only in 1953 that this was put to the test of a controlled randomised trial[6]. This was initiated in Manchester, England, the first ever controlled randomised trial in the management of cancer of the female breast[6].

Despite his epic discovery, Beatson was a conservative surgeon, subscribing to the view of his day that breast cancer was due to a 'continuous and excessive growth of the epithelium' of the breast which 'invades the surrounding tissue, spreads along the lymphatic vessels, passes from one set of glands to another'... and 'eventually forms deposits of disease in distant organs and parts of the body'[1]. This was the era of radical surgery. Lister, in whose wards Beatson had been a student and house-surgeon, had shown in 1865 that by using carbolic antisepsis the axilla could safely be cleared of lymph nodes at the time of removal of the breast, an operation which he first performed on his own sister[7]. This Halsted perfected, on anatomical principles, as a standard radical mastectomy in which both pectoral muscles were also removed[8]. Although Halsted's primary objective was to guard against recurrence, many of his cases being at an advanced stage. He subsequently reported that if '3 years had passed without detecting either local recurrence or symptoms of internal disease, one could feel assured that cure had been achieved'. His assumption was false. Long-term follow-up studies of patients with breast cancer have revealed that even 30 years following radical local treatment, patients with 'early' breast cancer still die from metastatic disease[9]. As was stated by Brinkley and Haybittle breast cancer is a disease which 'disseminates early but may recur late'[10] - or as was indicated by Keynes 'the invaders are bound to gain the upper hand in the end'[11].

One hundred years on

As Beatson stated, breast cancer starts in the 'epithelium of the breast', which now is accepted to be that which lines the 'terminal duct-lobular units' – the secretory acini[12,13]. It is likely, but yet unproven, that a series of changes precede transformation to the cancer phenotype. These include uncontrolled proliferation and the development of atypical cellular features which occur as a result of genetic changes. It is believed that the development of cancer is due to a series of multiple 'hits' on the genome and a large number of somatic mutations have been described in breast cancer cells. These include overexpression of the oncogenes c-myc, int-2 and c-erbB2, and loss or mutations of probable tumour-suppressing genes on chromosomes 1p, 1q, 3p, 11p, 13q, 17p, 17q, 18q[14]. Of these loss of p53 on chromosome 17p may be the most important. Initially the cancer cells may be confined to the breast lobules and ducts as 'in situ' disease but they later may develop invasive properties. Then they lose their attachment to neighbouring cells, degrade and invade the extracellular matrix, penetrate vascular and lymphatic channels, interact with a target vessel and extravasate into a new host tissue where they proliferate, become vascularised to form a metastasis[15]. These effects are also believed to be due to changes in the genome which either 'turn on' metastasising genes, eg. by expressing degrading enzymes, or delete or mutate a metastases suppressing gene, such as nM23[16,17].

Although breast cancer invades and metastatising early in its natural history, the time at which these micrometastases become clinically evident depends upon the aggressiveness of the tumour as well as its duration. Aggressiveness is variable – 'doubling times' range from 20 to 209 days according to the degree of differentiation or 'grade' of the tumour[18,19]. Tumour size is a product of time, and as this increases so does the potential for metastases, as demonstrated by the relationship between size, axillary involvement and the later development of metastases[20,21]. The smallest clinically detectable cancer approximates 1 cm in size. This contains one billion cells, which, assuming that the growth of the tumour initially is exponential, would take 5-15 years to replicate from a single transformed cell. During this time the disease is 'sojourning' in a 'pre-clinical' phase.

Two approaches, both of which are now known to reduce the mortality of the disease, have been developed. These are:

i. the treatment of micrometastatic disease by systemic therapy, given as an 'adjuvant' to local treatment and
ii. 'going back in time' by detecting the disease during its pre-clinical 'sojourn' phase by screening mammography.

Adjuvant systemic treatment

As has been indicated above, the first controlled randomised trial of systemic therapy in operable breast cancer was to determine the effect of ovarian irradiation as an 'adjuvant' to radical mastectomy[6]. Subsequent forms of 'adjuvant' systemic therapy include tamoxifen and multi-agent chemotherapy. In 1992 a meta-analysis of 133 randomised trials with over 75,000 women was reported by the Early Breast Cancer Trialists' Collaborative Group which unequivocally proved that ovarian ablation performed below the age of 50, the administration of tamoxifen for at least 1 year, and at least 6 cycles of multiple agent significantly reduced relapse rates and prolonged survival (Table I). Longer periods of tamoxifen use (2 years or even 5 years) were significantly more effective than shorter periods, but there was no difference between the effects of regimes of chemotherapy given over 6 or 12 months. Although in absolute terms the mortality differences may appear modest, they have persisted for at least 10 years, and worldwide represent an annual reduction of 150,000 deaths[22]. The need to administer systemic therapy must now be considered in all patients with early operable breast cancer.

Mammographic screening

It was recognised 50 years ago that clinically occult cancers of breast could be visualised radiologically[23,24]. But it was only with technical developments leading to improvement in the quality of film-screen mammography during the 1960s that it became accepted that breast cancer could be visualised radiologically many months before it became clinically evident[25]. In 1963 a randomised trial of mammographic screening of normal women was initiated in New York[26], this being followed by seven

Table I
15-years outcome of trials of ovarian ablation in 200 women with operable breast cancer under 50 years of age when randomised. (Redrawn from The Lancet; 1992, 339: 12 with permission)

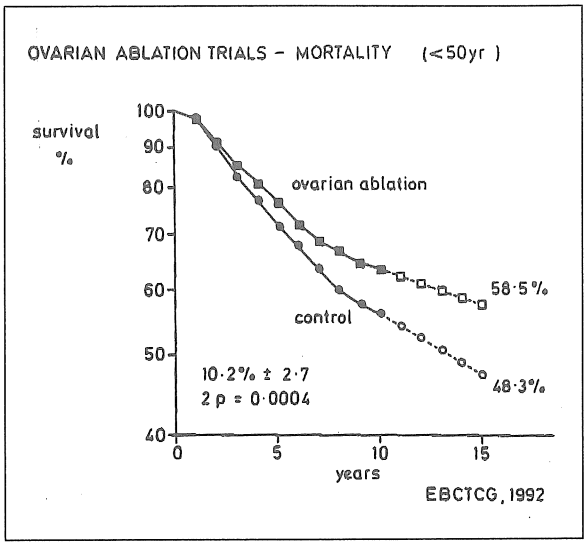
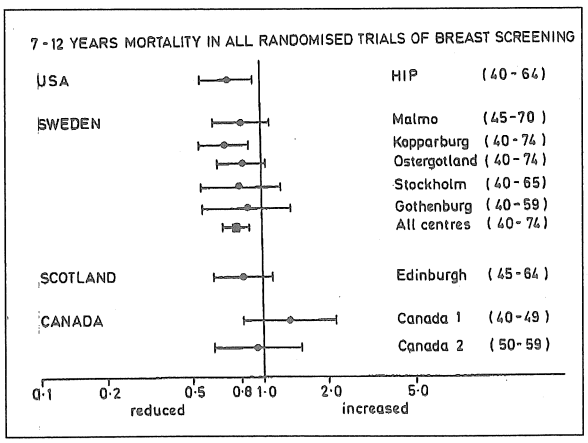


Table II
7-12 years mortality in all randomised trials of population screening by mammography. Odds of death with 95% confidence limits are given for each trial and for the overview of Swedish trials. Constructed from results given in refs 33-36



other randomised trials conducted in Sweden, Scotland and Canada which include over half a million women[27-32]. An independent overview analysis of the 5-13 year results of the four Swedish trials, and a meta-analysis of the 7-18 year results of all trials now indicate a highly significant reduction in breast cancer mortality in women of 50 years of age or more who are invited to attend for screening each 2-3 years[33,34]. In women over 50 years of age the annual reduction in mortality approaches 30%. Although some suggest that with longer periods of follow-up, a mortality reduction is beginning to emerge in younger women, this would not appear sufficient to recommend a change of policy in those countries which have set up national programmes of population screening which are restricted to women aged 50 years or more[35,36].

Like several other countries in Europe, UK initiated a programme of mammographic screening, this in 1988 in which women aged 50-64 years are invited to attend for a screening mammogram each three years[37,38]. It is essential to appreciate that screening by mammography is not a diagnostic test, but only differentiates a normal from an abnormal mammogram. Those with abnormalities must be further investigated by additional diagnostic tests, which may include a biopsy. Because it was necessary to ensure that these diagnostic tests were of high quality, the British Government included in its breast cancer screening service all the necessary back-up facilities for the assessment and diagnosis of abnormalities, their treatment, and the counselling and after-care of women. Those in whom an abnormality is detected on the initial screen return to the screening clinic, for their further tests, a unique situation in breast cancer screening. There they are in the hands of an expert multidisciplinary team, whose efficiency is subject to continuous monitoring, rather than, as in other countries, being referred to an independent practitioner who may or may not be experienced in the assessment of mammographic abnormalities. Increasingly multidisciplinary breast-care teams also are becoming responsible for the treatment of symptomatic as well as screen-detected cancers in UK.

Local therapy

During these developments there has been a radical change in local treatment.

Recognition that breast cancer can be cured by local therapy only when it is limited to the breast has resulted in a change of objectives. These are now to achieve local control of the disease and prevent local recurrence with minimal morbidity. This can equally be achieved in suitable cases by local excision of the tumour combined with radical radiotherapy to the breast, thus avoiding mastectomy. There are now six randomised trials including over 4000 patients which have compared a breast-conserving policy with mastectomy and which indicate that survival is the same[39]. Most prominent of these are the Milan and NSABP trial[40,41]. A re-analysis of the NSABP trial, which was confounded by the inclusion of ineligible cases, is now available from the National Cancer Institute[42]. If recurrence in the breast is included in local relapse rates, these are higher than with mastectomy, but breast recurrence can be treated by further excision or mastectomy without compromising the duration of life.

The treatment of breast cancer by local excision and radiotherapy is not new – in 1920 Geoffrey (later Sir Geoffrey) Keynes had been 'entrusted' by Professor George Gask to conduct a 'clinical trial of treating breast cancer with intense radiation', this by the implantation of radium needles. Observing 'astonishingly good results' in 50 patients with locally advanced and inoperable disease, he extended this method of treatment, combined with local removal of the tumour to operable cases[11,43,44]. In 1936 he reported that the results in 250 patients were the same as those of radical mastectomy, which he considered to be 'illogical and mutilating'.

The patient

How do these advances affect the patient with breast cancer? There are three stages in the management of all cancers, **diagnosis** to determine the nature of the disease, **staging** to determine its extent, and **treatment** to eradicate it. These will be considered in turn.

Diagnosis

A patient reporting a lump in her breast should now be investigated by the 'triple' procedures of clinical examination, mammography and fine needle aspiration. If clinical examination uncovers a discrete breast mass, the mammogram shows a spiculated opacity, and the fine needle aspirate indicates that the mass is solid and demonstrates clumps of malignant cells in the smear, the diagnosis of breast cancer is not in doubt. This was the case in all but 6 of 1511 breast cancer patients reported from the Edinburgh Breast Unit[45]. It is essential to appreciate that in a patient with a palpable mass in the breast, a report of a 'normal' mammogram does not exclude a cancer. Nor does a 'benign' report on an aspirate. If any one of these three tests is suspicious of cancer, further action must be taken.

If reliable results are to be achieved from fine-needle aspiration, the aspiration as well as the interpretation of the smear must be carried out by experienced personnel. The independent practitioner who only occasionally aspirates a breast mass, makes only one pass through a tumour, prepares a smear without checking its adequacy and sends it to the laboratory hoping for a definitive result, would be better to obtain a core biopsy using a Tru-cut needle.

This triple procedure is equally appropriate for a patient referred on account of an abnormal screening mammogram. The only difference is that the mammogram has come first. First the breast should be carefully palpated by the clinician, who being aware of the area in which the abnormality is present, can concentrate his attention on that segment of the breast. If the suspected abnormality is not palpable, further imaging will be required. Should it take the form of a discrete opacity, the radiologist is likely to wish to scan it ultrasonically; as a non-echogenic cyst can readily be aspirated by slipping the needle down the side of the transducer. If the opacity is solid, or if there is an architectural disturbance or cluster of micro-calcifications, magnification films are taken. These may well confirm the benign nature of the lesion, in which case it can be left alone, or indicate that, on account of marginal speculation, it is likely to be a small cancer.

The third procedure, fine needle aspiration, should now be performed on all solid non palpable lesions, but this requires the use of a stereoscopic radiological localisation device. In a report from Stockholm, 2,005 women with non-palpable mammographic abnormalities without mammographic or cytological suspicion of cancer were observed for a period of 2-6

years during which only one a cancer had been missed[46]. As in palpable disease this demands the expertise and experience of a multidisciplinary team, such as those developed for the support of the UK screening programme.

As a result of the availability of these investigations, open surgery should now be used predominately to treat a proven cancer, and less frequently to perform a diagnostic biopsy. In a closely monitored service, a surgical biopsy should be required only for borderline lesions. The biopsy rates reported from the UK national screening programme of less than 1% of screened women contrasts greatly with those from US[44]. In the large Breast Cancer Detection Demonstration Project in which over quarter of a million women attended for mammography and individual radiologists and surgeons assessed mammographic abnormalities, the biopsy rate was 9.9%![47]. Although this was before the development of stereotactic fine-needle aspiration, the value of this technique is still disputed in the United States, where high biopsy rates are still being reported[48,49].

If a biopsy of a non-palpable lesion is indicated, this should be carried out by a surgeon experienced in localisation techniques so that the breast is minimally disturbed. Otherwise subsequent mammography may be difficult to interpret. Radiologist and surgeon must work closely together. The insertion of a guide-wire by a radiologist in his office or clinic with the patient then travelling to the surgical operating room, is not good practise. It is clearly the surgeon's responsibility to confirm that the lesion has been removed, for which immediate radiology of the specimen is mandatory.

The pathologist must have an opportunity to obtain the unfixed specimen fresh so that he can radiograph slices and define the exact site of the lesion. The interpretation of these small lesions requires time, skill and experience, and frequently a second opinion will be necessary. Review sessions at which the pathologist discusses his findings with radiological and surgical members of the multidisciplinary team, are critical to maintain quality and it is regrettable that some radiologists and surgeons still accept that the assessment and if necessary removal of these small screen-detected abnormalities can be undertaken as an occasional responsibility.

Extent of disease and choice of treatment

In women with breast cancer these next two steps now overlap. The TNM staging system has been traditionally used to determine the stage and operability of breast cancer[50]. But routine radiological and biochemical investigations are insufficiently sensitive to detect occult metastatic disease, while the local criteria used to determine inoperability – a tumour over 5 cm in diameter, one with skin involvement or deep fixation, or one associated with palpably fixed axillary nodes – are relevant only for late-stage disease. In locally 'staging' the tumour the surgeon must now also consider whether it is suitable for breast-conserving therapy. He requires to use accurate criteria to determine appropriate size in relation to the size of the breast, which is best assessed in association with the radiotherapist. Pre-operative mammograms are essential to ensure that there are no multifocal deposits of tumour, or that widespread microcalcifications indicate extensive in situ change. Both contraindicate breast conservation. Following local excision of the tumour the surgeon must also ensure that the margins of the specimen are free of microscopic disease. This requires that he marks the orientation of specimen by clips or sutures and ink-marks its margins so that the pathologist can determine completeness of removal.

Local therapy

Now most small cancers can safely be treated with preservation of the breast. If the tumour is considered unsuitable for conservation therapy, or should the patient have a preference, mastectomy may still be indicated. Then the patient must be informed that breast reconstruction is an option. Ideally this should be performed at the same time as her mastectomy, either by insertion of an expansion prosthesis or by a musculocutaenous flap[51]. But only if surgeons with the required experience are available, as is now should be the case in dedicated Breast Units.

Systemic therapy

It has already been indicated that ovarian ablation, tamoxifen and multiple agent chemotherapy, given as

'adjuvant' systemic therapy for the management of primary breast cancer, reduce mortality[22]. Two decisions require to be made: which patient should receive systemic treatment, and which form should it take.

The likelihood of occult micrometastatic disease depends upon the size of the tumour, its histological type, its nuclear or cytological grade (defining its degree of differentiation) and the state of the axillary lymph nodes, involvement of which is proof of micrometastatic disease. For those patients with large tumours, tumours of low grade and those with axillary metastases systemic therapy is indicated. Sampling of the axillary nodes for histological examination provides essential information for the further treatment of the patient, which can readily be combined with the local excision of the tumour or mastectomy. For therapeutic purposes a complete axillary node dissection may be preferred. Lympho-vascular invasion in the operative specimen is a clear indication for systemic therapy.

When the tumour is small, or well differentiated and when there is no evidence of lymphatic invasion there is difficulty to know what is best for the patient. A large range of biological 'prognostic indicators' is now being explored (Table II), but while they may differentiate between groups of patients as regards outcome, they are not yet of great value for decision making in the individual patient[52-54]. Some oncologists do consider that those with tumours with poor oestrogen receptor and high epidermal growth factor receptor contents, which prognostically fall into a 'bad' group, should receive systemic therapy.

The choice of therapy can be guided by the oestrogen receptor (ER) content of the tumour. Should this be poor, the tumour is unlikely to respond to antioestrogen therapy. In a Scottish trial, premenopausal women with axillary node-positive disease were randomised to receive either 6 cycles of chemotherapy with cyclophosphamide, methotrexate and 5-fluoruracil (CMF) in standard dosage or to have their ovaries removed or irradiated[55]. While recurrence and survival rates were identical in the two treatment groups, correlation with ER concentrations in the tumour revealed that ovariectomy favoured those with ER rich, while chemotherapy favoured those with ER poor tumours. A similar trend is apparent in the report of the International Breast Cancer Study Group. From the meta-analysis of all trials it appears that tamoxifen also provides greater benefit in women with ER rich disease. This overview also suggests that there may be an advantage in giving combined chemo and anti-oestrogen therapy. This should become apparent with reports of other trials which are studying this specific problem[56].

Counselling

It should be clear that if a woman with breast cancer is to participate in the decision making process, which is her right, she must be informed of the options available to her. In a Scottish survey, we were appalled to find how little the average woman knew about the nature of breast cancer, its cause and the impact of early diagnosis[57]. A recent survey of young women in North Carolina suggests that even in the US, where women are more health aware, young women grossly overestimate the risk of contracting the disease, and have exaggerated views on the impact of mammographic screening[58]. One suspects that in Malaysia public knowledge is no better.

In those specialist breast units which have developed in UK, the role of counselling is well established. This also was recognised within the National Breast Screening Programme in which trained counsellors participate. The importance of a counselling service to women from the moment of diagnosis of breast cancer cannot be overemphasised. Trained professional counsellors, usually nurses, are now full members of the breast care team, play an invaluable role in helping women understand the alternatives available and in discussing the need for an opportunity to participate in decision-making. In Malaysia volunteers partly fill this role, but considering the complexity of this disease and its management they cannot replace the fully trained health professional, who has the basic knowledge and understanding to recognise what a woman requires to know, and can speak to her, if asked, with experience and authority.

In UK, a country with a well-developed National Health Service, it is now being formally recommended by specialist groups that the care of breast cancer should be the responsibility of specialist multidisciplinary teams – clinic doctor, radiologist,

cytologist, histopathologist, physician, surgeon and nurse counsellor[59,60]. The development of this team approach is facilitated by the system of health care, within which the professional and financial aspirations of the individual practitioner are submerged in the interests of the patient, who then is provided with a more skilled, efficient and caring service.

Risk and its preventation

Compared to women in which the incidence of breast cancer increases steadily during life, the disease is rare in males, who account for only 0.7% of all cases[61]. Active ovarian function is a necessary pre-requisite for the development of the disease. Women who have had an artificial menopause before the age of 35 years have one third of the incidence of women whose ovaries remain intact until their natural menopause[62].

The age at menarch, as also at menopause, affects risk, this apparently being related to the number of ovarian cycles a woman has during her reproductive life[63]. Each cycle would appear to contribute about 3% to the risk of later development of breast cancer. It is well established that the sooner a woman has her first full-time pregnancy the less is her risk of breast cancer[64]. So also does older age at last pregnancy reduce risk, as does multiple births[65,66]. Whether these effects are due to cessation of ovarian cycles during pregnancy, or to the increased differentiation of stem cells which occurs during full lactational development of the breast is unclear[67].

Knowledge that the development of breast cancer is dependent upon functioning ovaries has led to a number of preventative strategies aimed to reduce endogenous oestrogens in those women believed to be at greater risk from breast cancer. Of greatest application at the present time is the prophylactic administration of the antioestrogen tamoxifen[68,69]. In UK, a multicentre trial is being conducted under the auspices of the UK Coordinating Committee for Cancer Research to evaluate the role of tamoxifen in the prevention of breast cancer in high-risk women. In women over 45 years of age who have a first degree relative who with the disease, who have had a previous breast biopsy particularly when this shows atypical changes, and various combinations of these factors are being randomised to receive tamoxifen or a placebo[70]. Women younger than 45 years of age are included only if they have one or more first degree relatives who have developed breast cancer under the age of 50, particularly if bilateral, which is an indication of likely inheritance. The sequencing of the BRCA1 gene and discovery of the locus for a BRCA2 gene in kindreds with a dominant inheritance of breast cancer should give a lead to better definition of risk, at least in a proportion of cases[71,72].

Knowledge that maximum proliferative activity in the breast occurs during the luteal phase of the ovarian cycle has led to the suggestion that both oestrogen and progesterone are concerned with promoting the development of a cancer[73,74]. A feasibility study is being conducted in which ovarian function is reversably ablated in young women by gonadotrophin-releasing hormone agonists. A small and titratable amount of 'unopposed' oestrogen is administered to maintain good health. It is suggested that not only will this regime provide efficient contraception, but that it should substantially reduce the incidence of breast and ovarian cancers. Risk of endometrial cancer is obviated by intermittent administration of progesterone[74].

Dietary fat consumption has long been known to correlate geographically with breast cancer incidence in different countries; the rising incidence of breast cancer in Japan is reported to correlate well with the increased consumption of pork fat[75,76]. Reduction in dietary fat is known to reduce biologically available oestrogens in women, and a dietary intervention study to study the effect of this form of intervention is under way in US[77,78].

There has recently been great interest in the effect which diets rich in vegetables may have on the biological availability of endogenous oestrogens and their metabolism. This is believed to be due to their content of lignans, phyto-oestrogens and indole-carbones[79,80,81]. A case-control study from Singapore reported that in premenopausal women, diets which were rich in green vegetables and soya products reduced the risk of breast cancer[82]. These effects demand urgent exploration in this country, where vegetables form so large a proportion of dietary constituents.

Breast cancer in Malaysia

It is well established that the incidence of breast cancer in developing eastern countries remains lower than in the West. That in Thailand is reported to be only about one tenth of that in UK[83]. The Singapore registry currently reports an incidence of breast cancer which approximates one half of that in Australia and in the West, but there is concern that, as in Hong Kong and Japan, this incidence is on the increase[72,75]. This is also believed to be the case in Malaysia, but without accurate cancer registration, available evidence can only be regarded as anecdotal.

According to the Singapore Registry, the incidence of breast cancer varies between the races, Malays having a lower incidence than either Chinese or Indians[83]. A similar trend has been observed in Penang, where a regional registry has been established[84]. Whether this trend is due to reproductive or dietary habits, or other environmental factors, is unknown, but there is some evidence from studies in other countries to support a difference in risk of breast cancer between rural and urban dwellers[85,86]. Dr Freda Alexander (Edinburgh), Saroja Millott and I, in association with Dato' Suseela Nair and Professor C H Yip have been conducting a case-control study to determine whether differences in early life-style between the races may relate to breast cancer risk, but this can only provide preliminary data.

As Malaysia reaches for full development, those factors which explain racial differences in breast cancer risk are likely to become blurred. It would appear wise to explore them now.

Conclusion

In this paper I have indicated the changes which have taken place in our understanding of the natural history of breast cancer, and how these are being applied to the management of women with the disease. Before breast cancer can be truly prevented we must know its cause and which factors may protect against risk. This can only come about by an increased emphasis on research. Unless this is actively encouraged during Malaysia's growth to full economic development, a unique opportunity to unravel some of the factors which lead to this disease may be lost.

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MCQS For Breast Cancer : 100 Years on – What We Have Learned

1. Regarding the role of adjuvant systemic therapy for operable breast cancer
   a) The first randomised trial of adjuvant systemic therapy was to determine the effect of ovarian ablation
   b) In women with node-negative disease there is no indication for systemic adjuvant therapy
   c) A twelve-month course of chemotherapy with CMF has been shown to effect a better mortality reduction than one lasting 6 months
   d) Ovarian ablation and tamoxifen are more likely to benefit patients whose tumours have poor concentrations of oestrogen receptor
   e) In premenopausal women with node-positive disease chemotherapy with CMF has been shown in a randomised trial to be more effective than ovarian ablation

2. Regarding the genetics of breast cancer
   a) The disease is believed to be caused by a single genetic hit
   b) p53 is a tumour-suppressor gene
   c) BRCA1, which is situated on chromosome 17, is mutated or lost in all women who show a true hereditary predisposition for breast cancer
   d) c-erbB2 is an oncogene
   e) nM23 is a gene which evokes invasive properties in cancer cells

3. Concerning the local therapy of breast cancer
   a) Randomised trials in women with stage I and II disease indicate that local excision with radical postoperative radiotherapy gives reduced survival compared to treatment by mastectomy
   b) Local recurrence following treatment aimed at conserving the breast is most common in the ipsilateral breast
   c) Mammography should be regarded as an essential investigation before embarking on breast conserving treatment
   d) Mastectomy is preferred treatment for those with large (over 4cm) tumour
   e) Breast reconstruction may predispose to hypersensitivity states

4. When considering the methods of diagnosis of breast cancer
   a) In a patient with a palpable abnormality of the breast normal mammographic appearances can be taken to rule out cancer
   b) The 'triple' diagnostic procedure (clinical examination, mammography and fine-needle aspiration cytology) makes a positive diagnosis of cancer in over 95% of patients with palpable disease
   c) Mammographic screening has been proven in randomised trials to reduce mortality from breast cancer in women 40-49 years of age
   d) A symptomatic cancer if the breast is typically associated with a spiculated opacity on a mammogram
   e) Breast-self examination is the recommended screening method in UK

5. Concerning 'prognostic factors' in node negative breast cancer
   a) Tumour size is a time-dependent variable
   b) S-phase fraction refers to the proportion of cells which are in the mitotic phase of the cell cycle
   c) c-myc is a marker of apoptosis
   d) Cathepsin-D is a proteinase
   e) Angiogenesis factor is believed to be analogous to platelet-derived growth factor (PDGF)