National Seminar on Breast Cancer

A P Forrest

The second National Seminar on Breast Cancer was held in Kuala Lumpur on 10th January 1996 under the joint chairmanship of Dato' Suseela Nair (Director, KL Hospital Breast Clinic) and Prof Sir Patrick Forrest (late Associate Dean, International Medical College and Visiting Professor to Universiti Malaya) under the sponsorship of the Ministry of Health. The Seminar was officially opened by the Minister of Health, Dato' Chua Jui Meng. Forming a pre-congress Workshop of the XI Asian Pacific Congress of the International College of Surgeons, it attracted a wide audience who listened to a series of authoritative papers given by a panel of international speakers from Malaysia, Europe and Australia whose travel was generously supported by the British Council, Johnson and Johnson, Siemens Medical Division, Zeneca UK and Farmacia. Several of the speakers also participated with local surgeons in Symposia on Benign and Malignant Breast Disease which formed part of the main Federation Congress.

The National Seminar opened with a description, by Dato' Dr Suseela Nair of 'Breast Cancer in Malaysia'. Although the incidence of the disease approximated one half of that in the western world, it was on the increase, particularly in young women. The peak prevalence in women attending her clinic in KL Hospital was between ages of 30-49 years compared to 50-60 in the west. As a result an unusual number of cases presented during pregnancy, which posed particular problems regarding appropriate treatment. Similar data had been published from University Hospital by Associate Prof Yip Cheng-Har. According to Dato' Suseela Nair, the prognosis in these young women was unfavourable, this due mainly to delay in presentation as a result of a low index of clinical suspicion, poor sensitivity of mammography and women first seeking cure by traditional medicine. Increased biological activity of the tumour could not be discounted. In a subsequent paper given during the International College meeting, Dato' Nair described the various forms of traditional medicine available to her patients, and the profound effects which these could have on the stage of the disease at presentation to hospital. Eighty per cent of her patients presenting with late-stage (III and IV) disease had first consulted a bomoh or other 'medicine man'. She strongly recommended that women with breast cancer should first seek orthodox treatment and only when this had been completed seek such additional support as traditional methods might provide.

Intensive public education was improving the stage at which women presented to her clinic. In 1991, 70% of women had late stage (III and IV) disease – by 1994 this proportion had fallen to 42%. In those western countries with active screening programmes, the large majority of women now presented with disease of early (I and II) stage.

Although the proportions of patients attending the KL Hospital breast clinic were identical amongst the three races, this finding contrasted with a report from University Hospital, where the disease presented less commonly in Malays compared to Chinese and Indians. This impression agreed with incidence rates recorded in the Cancer Registries in Singapore and Penang. Accurate cancer registration in Malaysia is desirable.

Non-invasive breast cancer

Of the two forms of non-invasive (in-situ) breast cancer – lobular and ductal – only the latter (ductal carcinoma in situ – DCIS) represents a true malignancy. Lobular carcinoma-in situ is but a marker that the breast is at increased risk of cancer. Although DCIS is not yet an important entity in Malaysian women, the introduction of mammographic screening in western countries has resulted in a great increase in the frequency of its diagnosis. Dr Jan Hendricks, Director of the National Expert and Training Centre for Breast Screening in Nijmegen, The Netherlands,

indicated that in the Netherlands some 15-20% of cancers detected through screening were of non-invasive ductal type. Unlike lobular carcinoma-in situ which is diagnosed only on histological examination, DCIS is associated with visible microcalcifications on mammography which now provide the most common diagnostic feature. Dr Hendricks stressed that magnification views were essential to define the distribution and extent of these microcalcifications which can be further defined by digitisation of the mammographic image and computer analysis.

There was good correlation between the type of cancer and the appearance of the microcalcifications. Those which were poorly differentiated (so-called 'comedo type') are associated with linear branching coarse granular calcifications which lie in the central necrotic zone of the tumour within the small ducts whereas in those of well differentiated type (micropapillary and cribriform) the microcalcifications are finely granular and dispersed in clusters. As the likelihood of the development of invasive cancer in the affected breast was influenced by the degree of differentiation, it was important that the surgeon recognised the significance of these appearances when performing his localisation biopsy, for which the insertion of a hook wire using a stereotactic device was necessary. Mammography usually underestimated the size of the lesion, particularly of the well-differentiated lesions, but in 80% of cases the discrepancy was less than 2 cm provided 'state-of-the-art' mammography was available.

In describing the histopathological appearances of DCIS, Dr Michael Bilous, Department of Pathology, Westmead Hospital, New South Wales, indicated that DCIS was characterised by the proliferation of atypical duct epithelial cells which did not traverse the basement membrane to invade the surrounding stroma. Noting that autopsy series had shown an incidence of unsuspected DCIS in 10-15% of clinically normal breasts, he believed that the great increase in incidence detected in screening programmes (10-40% of malignancies) had highlighted deficiencies in our knowledge of the disease, particularly regarding its natural history and pathology. Three large biopsy series had indicated that DCIS carried a risk of invasive cancer in the ipsilateral breast of 25-30% in 10+ years. Important issues to be resolved in diagnosis and management included the distribution of the disease – whether multifocal (limited to a segment of the breast) or multicentric (involving more than one quadrant), its histopathological subtype, and the influence on prognosis of proliferation indices (ploidy and S-phase fraction), oncogene products, and hormone receptors. The relative value of fine needle and core biopsy was being evaluated but remained to be defined. The lack of diagnostic concordance between pathologists was a matter for concern.

Dr Bilous believed that the traditional classification of DCIS into 'comedo' (poorly differentiated) and 'non-comedo' (well differentiated) types was an oversimplification, and a number of other classifications had been proposed to include nuclear grade, and the presence or absence of necrosis, factors which were known to affect its natural history. Nuclear grade was of particular importance, high grade being associated with high proliferation indices, marked expression of c-erbB2, poor expression of oestrogen receptor, factors also known to carry a bad prognosis. Particular difficulty was experienced in differentiating between non-comedo DCIS and atypical ductal hyperplasia. He advised that meantime key factors such as nuclear grade, presence and type of calcification, architecture of the duct proliferation, size of lesion and relationship to excision margins should be documented in all cases. A multidisciplinary approach between pathologist, radiologist and surgeon was essential to our further understanding of this disease.

Dr Helen Stewart, Director of the Scottish Cancer Trials Office, in reviewing the current management of DCIS, indicated that when more than one quadrant of the breast was mammographically involved the disease should be regarded as 'extensive' and mastectomy advised. Although in these large lesions areas of micro-invasion were more frequent, mastectomy should prove curative in 90% of cases. For smaller lesions, most European surgeons now preferred a breast-conserving approach. Following local excision, clear margins were desirable but difficult to confirm, particularly of the specimen had been removed in more than one piece. A number of randomised trials were in progress to determine the role of radiotherapy and systemic treatment with tamoxifen – the UK trial, in which following complete

local excision of the lesion, patients were randomised to receive either one, both or neither of these treatments now included over 900 patients. Only one randomised trial had been reported, this the NSABP trial of local excision with clear margins versus local excision followed by radical radiotherapy which included 818 patients. A recent update had shown a significant increase in local relapse rates in those treated by local excision alone. It was uncertain whether treatment should vary according to histological type. In view of the later risk of invasive disease long-term follow-up was essential, particularly in those patients treated by local excision alone.

Mr Udi Chetty, Director of the Edinburgh Breast Unit, described his practice. When suspicious calcifications were present it was first necessary to make a definitive diagnosis, for which he preferred an open biopsy. As the architecture of the tumour could not be determined on fine-needle aspiration, it could not differentiate between non-invasive and invasive cancer. For small lesions a localisation biopsy was necessary, his preference being for a hook wire inserted stereotactically. Insertion of more than one wire could help define the extent of the lesion. Specimen radiology was essential, and if the calcifications extended to the margins of the specimen further excision was required, unless the initial mammograms has indicated extensive DCIS, when following histological confirmation mastectomy was indicated.

The specimen should be orientated by 1-4 clips placed in each compass quadrant, and the margins inked. Should the histology indicated that in-situ disease extended to the margins, a further excision should be advised. At this stage, some women would prefer to proceed to mastectomy. There was no indication for axillary surgery in in-situ disease, and when performing a breast conserving procedure, Mr Chetty left the axilla intact. Should a mastectomy be indicated, he carried out a 4-node sample of the lower axillary nodes, so as to confirm node status in those patients with more extensive disease, in which foci of microinvasion were more common. In Edinburgh, all suitable patients were entered into the UK DCIS randomised trial, the results of which would provide evidence regarding the best form of management of this disease.

Invasive breast cancer: local therapy

Reviewing the evidence comparing mastectomy with local excision and radiotherapy, Sir Patrick Forrest referred to a recent meta-analysis of 9 randomised trials including over 4,000 women with operable disease which indicated that survival was identical. There were no significant differences in local or systemic relapse. A randomised trial from Milan comparing 'quadrantectomy' (removing at least 2 cm margins of normal breast, overlying skin and underlying pectoral fascia) with 'lumpectomy' (with a 1 cm margin of normal breast), both with axillary clearance and radical radiotherapy to the breast, had reported lower local relapse rates with the wider excision. Excision margins involved by tumour, extensive in-situ change within and surrounding the tumour and a young age also increased local relapse.

Four trials had been reported to determine whether, in favourable cases (eg. small node-negative tumours) radiotherapy may be dispensed with. While survival has not been compromised, local relapse rates in those treated by local excision alone had been unacceptably high, even in those with favourable disease. In the NSABP study, with tumours up to 4 cm, relapse in the ipsilateral breast was 43% after 9 years of follow-up. In a recent Scottish trial of local excision, in which systemic therapy with tamoxifen or chemotherapy was given to all cases, patients then being randomised for local radiotherapy, local relapse rates in those not irradiated approached 30% at 5 years. Radiotherapy must still be regarded as a necessary part of breast-conserving treatment for invasive cancer, irrespective of tumour size, type, or the administration of adjuvant systemic therapy.

Surgeons practising this form of management must work within agreed protocols in which breast and tumour size, mammographic appearances of multifocality and extensive in-situ change, and histopathological findings at excision margins were taken into account in deciding suitability. This requires that he/she was a member of a multidisciplinary team, which included a trained counsellor, so that the patient could be encouraged to participate in the decision making.

Dato' Suseela Nair indicated that women in Malaysia

were becoming more aware of the role of breast-conserving procedures. In 1991, 95-98% of women with operable breast cancer were treated by mastectomy – in 1994, 40% opted for conservation treatment. In her practice appropriate tumour size was usually restricted to < 2 cm, although if the breast was large peripheral tumours of up to 4 cm were also regarded as suitable for conservation therapy. Surgical axillary node clearance of levels II and III was routine; all patients with positive nodes who were less than 70 years of age were offered chemotherapy. Other than those with mammographically detected disease, radical postoperative radiotherapy was routine.

Dr Jan Hendricks stressed the importance of pre-operative high-quality mammography in determining suitability for breast conserving treatment. Tumour size could be accurately assessed, while the presence of multifocality or extensive in-situ change could be detected, indicating the need for mastectomy. By 3D simulation of digitised mammograms better definition of multifocality could be achieved. The role of magnetic resonance imaging was under study.

Dr Michael Bilous similarly stressed the importance of recording pathological features accurately, best by means of a structured synoptic report format. While a range of pathological prognostic data should be recorded in all patients, irrespective of treatment, certain special requirements were required when breast conservation was employed. The surgeon should place markers to orientate the specimen, and describe the location of the tumour in it. On receipt of the specimen the pathologist should paint the margins with ink or other pigment and should prepare blocks of the nearest margins(s) to the tumour and adjacent breast tissue. The amount of DCIS was an important predictor of local relapse; an invasive tumour with extensive intraduct component (EIC+ve) was that which contained 25% or more of DCIS within the main tumour together with DCIS in the adjacent breast tissue. A second form of EIC+ve tumour was one that was predominantly DCIS with foci of stromal invasion. Such tumours had local relapse rates of 34% and 40% at 5 and 10 years compared to 2% and 3% in those which were EIC-ve. Relapses which were believed to occur in residual DCIS at the site of the excised tumour, were equally likely to be invasive.

In describing his approach to the axillary nodes, Mr Udi Chetty indicated that there were two alternatives – axillary node sample with axillary radiation should involvement by metastatic tumour be proven, and total axillary node clearance, when axillary radiotherapy was not required. In Edinburgh, a randomised trial had been reported in which these two regimes were compared in 400 patients with operable disease treated by mastectomy. The incidence of positive nodes defined by these two procedures did not differ. Survival and recurrence of disease were also similar, except for a small increase in chest wall recurrence in those patients with positive nodes in the clearance group who did not receive radiotherapy. A similar trial had been instituted in patients currently being treated by a breast conserving approach. The incidence of involved nodes again was identical in the sampled and cleared groups. These findings agreed with a report from Milan, in which 'skip' lesions in the axillae of 777 node-positive cases were observed in only 1.2%. However, at least 4 nodes should always be taken in a sampling procedure.

A careful subjective and objective assessment of morbidity from axillary surgery was under way, this including arm volume, measurement of a range of shoulder movements and of muscle power. Preliminary findings indicated little difference between those treated by an axillary node sample or clearance, except that when positive nodes indicated irradiation of the sampled axilla there was a greater likelihood of early restriction of shoulder movements. This effect had largely dissappeared by 2 years. Mr Chetty believed that when an axillary clearance was indicated, this should include levels I to III, access to which was facilitated by division of the pectoralis minor muscle as in the original Patey technique.

Reviewing the evidence for postoperative radiation therapy following breast-conserving surgery, Prof Allan Langlands, Chairman, Division of Radiology, Westmead Hospital, New South Wales, believed that given that there was a consensus that survival was not compromised, patient choice was now a critical determinant of whether the breast should be preserved or not. The cosmetic result was of major importance and radiation morbidity should be minimised by normally fractionated techniques, usually 25 fractions

over 5 weeks. He advised the routine delivery of a 'boost' which allowed limitation of the dose to the rest of the breast, preventing fibrosis, and provided 'insurance' against variations in surgical techniques and pathological interpretation. The selection of a subset of patients in whom radiation can be omitted cannot be made from existing clinical trials, but required analyses of risks of recurrence and of costs and toxicity of radiation treatment in individual patients. In his series of 438 patients treated by breast-conservation with clear margins by many surgeons, only 32 patients had locally relapsed, 23 had relapsed within 5 years, 8 with simultaneous distant disease. His local relapse rate was 1% per annum, a figure in agreement with that reported from Milan.

In answer to a question on indications for radical radiotherapy following mastectomy, Prof Langlands believed this to be indicated in those with 10 or more positive nodes in their axillary clearance specimen. He believed strongly that the morbidity of uncontrolled disease in the axilla far outweighed that of post-radiation lymphoedema of the arm.

Invasive cancer: systemic adjuvant therapy

Dr Helen Stewart pointed out that it was only 20 years since the first report that systemic therapy, given as an adjuvant to local treatment, then mastectomy, increased the survival of patients with operable breast cancer. Three main forms of systemic therapy had been evaluated by Richard Peto and the Early Breast Cancer Triallists' Collaborative Group which had reported the results of a meta-analysis of 133 randomised trials which included over 75,000 women. This analysis had unequivocally proved that ovarian ablation performed below the age of 50 years, the administration of tamoxifen for at least 2 years in women over 50, and at least 6 cycles of multiple agent chemotherapy in both age groups significantly reduced relapse rates and prolonged survival. Indirect analyses suggested that longer periods of tamoxifen use (more than 2 years) were more effective than shorter periods, but there was no difference between the effects of chemotherapy given over 6 or 12 months. The results of the Scottish tamoxifen trial suggested that no additional benefit accrued from the administration of tamoxifen for more than 5 years. These effects were statistically significant and proportionally the same in node positive and node negative disease, although on account of its better prognosis, they appeared to be more modest in node negative patients. Dr Stewart reported studies indicating that the observed effect of tamoxifen on cardiovascular morbidity may provide additional benefit. In a recently reported Scottish trial ovarian ablation and chemotherapy gave equal overall benefit in young patients, but when oestrogen receptor status was taken into account, the outcome differed only in those treated by ovarian ablation, those with high levels doing better than those with low levels.

The question whether combinations of chemotherapy and antioestrogen therapy conveyed greater benefit than either alone was still unanswered, but the results of subject analyses suggest that this may be so, at least for tamoxifen in those postmenopausal women with high ER tumour levels.

In addressing the question 'What I advise', Prof Langlands suggested that adjuvant systemic therapy should now be considered for every women with operable breast cancer. In premenopausal women, he advised 6 cycles of CMF for all node-positive patients, as well as for those with node negative disease whose tumours were greater than 2 cm in size, had a high histological grade (grade III), vessel space invasion or oestrogen receptor negativity. In postmenopausal women, he believed chemotherapy has a relatively minor role and should be considered on an individual basis, his standard advice being to take tamoxifen 20 mg daily for 5 years.

In late stage (stage III) local disease, Prof Langland's regime was for 3 cycles of anthracycline-containing regimes followed by radical radiation. Following completion of local radiotherapy patients were given 6 cycles of CMF. He presented evidence that the results of this regime were equivalent to those which followed high dose chemotherapy and stem-cell rescue, which, in his view, had no role as adjuvant therapy outside randomised clinical trials.

Screening and prevention

In answer to the question 'Which women should be screened', Dr Jenny McCann (Research Scientist,

Department of Community Medicine, Cambridge) believed that until trials of screening younger women had demonstrated significant benefit, only women over 50 years of age should be included in organised programmes of population screening. She stressed that the UK programme should be critically monitored to determine why interval cancer rates were higher than in Sweden, and that measures should be taken to optimise compliance and cancer detection rates, particularly for small cancers. It was possible that the underlying incidence of the disease had been underestimated and that original targets set for cancer detection rates were too low.

The results of the UK trials on screening in women less than 50, on one versus two views, on frequency of screening and on single versus double reading would give guidance to future policy, which she believed should include the extended use of two views, mandatory double reading and possibly a screening interval shorter than 3 years.

During the Breast Cancer Symposium which followed as part of the International College conference, Dr McCann presented further information on the British programme of screening, in which women aged 50-64 years received personal invitations to attend for screening mammography every 3 years. Screening was originally by single-view mammography, but two views were now used at the prevalence screen. Compliance exceeded 70%. Notable in the UK programme was the provision of diagnostic facilities within the screening service, which was then responsible for the further investigation of abnormalities detected on the screening mammogram, including if necessary a surgical biopsy. She described in detail the arrangements for monitoring the screening process in East Anglia, contrasting interval cancer rates in that region with those elsewhere in UK and in Sweden. Revised targets proposed for the screening programme had been set at more stringent levels, and performance would continue to be rigorously monitored.

The 1993/94 results of the screening programme in UK have recently been published by the National Health Service. During the 12 months under review 1.6 million women attended for screening, a compliance rate of 72%. Recall rates for further tests were 6.5% for prevalence and 3.1% for incidence screens with biopsy rates of 0.87% and 0.46% respectively. Cancer detection rates for prevalence and incidence screens were 6.0 and 3.8 per 1000 women screened.

At this Symposium, Dr Jan Hendricks described the current screening programme in the Netherlands, which also had been designed for women over 50 years of age. By the use of 48 mobile units, each women could be screened within 8 km of her home. Women with abnormalities were referred through their family doctors to specialist breast units in regional hospitals. A recent national (NETB) report indicated compliance of 80%, recall rates of 1.3% for prevalence and 0.65% for incidence screens and cancer detection rates of 4.5-10 per 1,000 for prevalence and 3.0-4.8 for incidence screens. The positive predictive value of an abnormal mammogram was 50-60%. Dr Hendricks emphasised the importance of central quality control of mammographic techniques, which in Netherlands included daily checks on all film-developing units. He said that the cost of screening had been calculated at 80,000 Guilders (US$ 60,000) per life saved contrasting with that of the installation of seat belts in automobiles which was 1 million Guilders!

At the Symposium, Dr Osmo Rasanen, director of the Specialist Breast Detection Centre in Turku, Finland, referred to the Mama Programme of Breast Self-Breast Examination in Finland, which between 1973-75 had enrolled over 28,000 women. The strategy consisted of three elements – initial face-to-face instruction with issue of a 2-year diary card, continuous interaction between key lay personnel and women practising BSE and the provision of diagnostic mammography for those suspecting an abnormality. He reported that a linkage analysis with the Finnish Cancer Registry had shown that cumulative incidence of breast cancer over the 14 years from completion of the programme exceeded that expected by a factor of 1.2 and that there had been a significant reduction in breast cancer deaths. Some of this difference might be due to selection bias (twice as many women in the BSE population had a college education as did the general population) but he believed that the findings were consistent with a beneficial effect of instruction in BSE.

Dr Rasanen went on to describe the current

programme of mammographic screening in Finland, which had started in 1987. It was based on 30 specialist centres to which women of 50-64 years of age were invited for two-view mammography each 2 years. The assessment of mammographic abnormalities was carried out in these specialist centres, which functioned apart from the normal system of health care to which only patients, requiring treatment would be referred. In Finland, with its population of 5 million, 200,000 women were eligible to enter the screening programme.

The National Seminar ended with a discussion on preventive strategies by Sir Patrick Forrest who indicated that true prevention of the disease was feasible only when its cause was known. Current strategies relied on inhibiting the function of the ovaries, which was known to be an essential pre-requisite for the development and promotion of breast cancer. Ovariectomy before the age of 35 years reduced the life-time incidence of the disease by one third. Prolonging the period of ovarian function eg. by early menarche or late menopause increased risk. Pregnancies at an early age, and multiple pregnancies also decreased risk, but this effect might be due to cellular differentiation reducing susceptibility to carcinogens. Interventions aimed at reducing the availability of biologically active oestrogens in women believed to be at high risk from the disease were being actively pursued. Most prominent was the administration of the anti-oestrogen tamoxifen, and large randomised studies to determine the effect of tamoxifen in high-risk women were under way in Europe and US. Reduction of dietary fat (reducing biologically active oestrogens) was also under study, as was increase in vegetable products. Phyto-oestrogens in green vegetables and soya competed for endogenous oestrogens, while indole-C-carbones in brassicas directed the hydroxylation of oestrogen to form inactive metabolites. Analogues of vitamin A (retinoids) were known to inhibit proliferation of human breast epithelial and oestrogen-sensitive breast cancer cells, possibly through the oestrogen receptor. A trial was underway in Milan.

The feasibility of a proposal that ovarian function was inhibited in young women by gonadotrophin-releasing hormone analogues, providing safe contraception while profoundly reducing the incidence of breast and ovarian cancer, was being explored. Recognition that maximum proliferation of breast epithelium occurred during the luteal phase of the menstrual cycle had promoted the believe that oestrogen in the absence of progesterone did not stimulate epithelial growth. Were this so, the unpleasant effects of ovarian ablation could safely be prevented by the administration of oestrogen alone. Any additional risk from endometrial cancer could be prevented by intermittent courses of low-dose progesterone.

The discovery of the BRCA1 and BRCA2 genes has allowed the definition of risk in members of kindreds with autosomal dominant breast cancer. For families with breast and ovarian cancers, BRCA1 was the responsible gene. For those families with breast only cancers, BRCA1 and BRCA2 each accounted for 45% of women (and men) at risk; the remainder were apparently due to deletions or mutations of p53 or AT genes. These genes were apparently not involved in sporadic cancer, which accounts for over 90% of all cases.

There was some recent evidence that adverse life events may increase the risk of breast cancer, stressing the importance of a healthy and relaxed life-style for all women.

Questions

1. Comparing breast cancer in Malaysia with that in the western world
   a) The incidence of breast cancer is equal
   b) Women tend to present with more advanced ('late-stage') disease
   c) Local treatment is less likely to conserve the breast
   d) In-situ breast cancer is more common
   e) Women with the disease tend to present at a younger age

2. Concerning ductal-carcinoma-in situ-cancer (DCIS) of the breast
   a) When 'comedo' in type the prognosis is worse than when 'non-comedo'
   b) When non-comedo in type mammographic calcifications are finely granular and dispersed in clusters
   c) The mammographic appearances given an accurate impression of the size of the lesion
   d) Mastectomy is the treatment of choice
   e) An axillary node sample should be routine

3. Concerning the local treatment of breast cancer by breast conservation
   a) A randomised trial has indicated that wider margins of excision decrease local recurrence rates
   b) Orientation of the excision specimen by the placing of sutures or clips is necessary
   c) Extensive in-situ change is associated with reduced local recurrence rates
   d) An adequate axillary node sample requires that at least 2 nodes are removed
   e) Radiotherapy to the breast following local excision of the tumour is best given in 25 fractions over 5 weeks

4. Population screening by mammography
   a) Has been shown to benefit western women aged 50 years and over
   b) Is best carried out by single (one view) oblique mammography
   c) Leads to the recall of at least 10% of women for diagnostic tests
   d) Costs approximately US$60,000 per life saved
   e) Should be made widely available to Malaysian women

5. Regarding the factors which affect the risk of breast cancer
   a) An early menarche increases the life-long risk of the disease
   b) Tamoxifen inhibits the action of oestrogen on breast epithelial cells
   c) Retinoids are analogues of vitamin C
   d) Maximum proliferative activity of the breast epithelium occurs during the follicular phase of the menstrual cycle
   e) BRCA1 and BRCA2 are genes known to be related to the development of 'sporadic' breast cancer.