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Age and death in breast cancer

A young woman treated for early carcinoma of the breast has a greater chance of living long enough for her hidden micrometastases to progress and eventually kill her than an elderly woman with the same disease—who could die of, say, ischaemic heart disease or chronic bronchitis long before the cancer develops to produce its lethal effect. Thus breast cancer is popularly supposed to be a more aggressive—as well as a more tragic—disease in young than in old women, a hypothesis apparently supported by that equally popular pathological myth of the "atrophic scirrhous" cancer of the breast in old women.

Since we reviewed the evidence refuting this idea,[1] new evidence has appeared strongly suggesting that it is the old women whose breast cancer is the more aggressive. Mueller and his colleagues from McMaster University have carefully studied age as a determinant in the rate of dying and the cause of death in 3558 women whose records were collected over 19 years by the Syracuse Upstate Medical Center Cancer Registry.[2] During this time just under half the patients died, 88% from carcinoma of the breast. As might be expected, 96% of the deaths in the 21-50-year-old age group were attributed to the breast cancer, but only 77% in the age group 71 and over. The rate of dying in all age groups could be described by two single exponential functions. Those who had presented with stage III disease showed a rate with an initial rapid fall, distinct from that of the women presenting with stage I and stage II disease. Different rates emerged clearly, however, for each age group. For example, half of the eventual deaths from breast cancer occurred within 11·5 years for ages 21-50, 7·2 years for 51-70, and 4·0 years for 71-100. Thus if all other causes of death were ignored the breast cancer appeared to be more rapidly lethal the older the patient. This applied even to those dying of breast cancer who had initially presented with stage I disease: 60% survived for 20 years if they had been under 50, whereas only half of those over 70 were alive at six years. Emphasising that in the past the lethal property of breast cancer in the elderly has been masked by computations of relative survival rates, Mueller and his colleagues summarise their findings by stating that most women who develop carcinoma of the breast are likely to die of their cancer—which has indeed wide support in current publications[3 4]—but that the rate of dying in the younger age group is significantly slower than that in the older age group.

What, then, is the biological and clinical importance of this surprising finding? Firstly, given the biology of the disease, the prognosis for any individual cancer must be a complex function expressing the interrelationship of many variables. The time of diagnosis, the stage of the disease, the method of treatment, factors relating to the interaction between patient and tumour, the presence or absence of oestradiol receptors, the invasive properties of the tumour, and perhaps many other, unknown biological variables all contribute to the final outcome. How could age affect any of these factors? The study reported, of course, corrected for stage at presentation, and as yet no one therapeutic regimen has emerged as superior to another; so we must postulate some intrinsic difference in the tumours themselves or the patient's response to the tumour.

Immune mechanisms wane with age,[5] and one attractive hypothesis is that the tumours in each age group are identical but that the elderly patient is less able to inhibit their dissemination. We must also consider the alternative hypothesis, that the tumours themselves are intrinsically different. One difference is that the mean concentration of oestradiol receptors is higher in postmenopausal women than premenopausal women.[6] Patients with oestradiol-receptor-positive tumours, however, have a better prognosis regardless of clinical or pathological stage.[7] Clearly we need more research on other biological variables of breast cancer in relation to age.

Adjuvant chemotherapy for patients with diseased axillary nodes significantly reduced the recurrence rate and prolonged the disease-free interval during the early stages of follow-up in premenopausal women alone, with a non-significant though similar trend in the older age group[8] (though this age distinction did not appear in a later study[9]). This has led many workers to believe that the benefits conferred by adjuvant chemotherapy are indirectly related to a chemical "endocrine ablation."[10] Bonadonna and Fisher,[11] however, have suggested that an alternative explanation for the findings might be the different biological properties of the cancers in the two age groups, the older women perhaps possessing a more aggressive type of disease. Now there is evidence to support their hypothesis. If this is substantiated, we should consider trials of an alternative and perhaps more aggressive strategy of systemic treatment for the older women with apparently early breast cancer.

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[9] Bonadonna, G, *et al*, *New England Journal of Medicine*, 1976, **294**, 405.
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Premenstrual tension syndrome

There is nothing pleasant about menstruation. At best it is a physiological inconvenience; at worst it contributes to chronic ill health through menorrhagia and dysmenorrhoea, and there are other associations. Frank[1] and more recently Dalton[2] have described a premenstrual tension syndrome with a wide range of physical and psychological symptoms. Clare[3] has suggested that the syndrome is not a single entity but that various "symptom profiles" occur in different combinations, some responding to one treatment and some to another. Whatever the symptoms there is a common, predictable relationship to menstruation, and this suggests a hormonal basis.

Frank,[1] one of the first to link premenstrual symptoms with the second half of the menstrual cycle, postulated an imbalance between the ovarian steroids oestradiol and progesterone. Others[4–6] have supported this view, but evidence of progesterone deficiency in the second half of the cycle has been based largely on clinical observations,[7] and only recently have radioimmunoassay techniques brought a new accuracy to the measurement of steroid hormones. A group working at St Thomas's Hospital showed a lack of progesterone in the second half of the cycle in 30% of women suffering from severe symptoms when compared with normal controls.[8 9] Similar results have been reported elsewhere,[10] but what of the 70% of women with normal progesterone values? Some may have raised oestradiol concentrations, but there is no evidence that women with prolonged or high oestrogen activity (such as occurs in metropathia haemorrhagica) suffer unduly from premenstrual tension.[7] More likely is a relatively minor imbalance in hormones including not only oestradiol and progesterone but also aldosterone and prolactin. The results so far reported have been conflicting. Brush's[8] work on plasma aldosterone concentrations in patients suffering from premenstrual tension showed no significant abnormalities. Raised prolactin concentrations have been claimed to account for at least some of the wide range of premenstrual symptoms,[11–13] but other investigators have failed to confirm any rise in prolactin concentrations in patients with premenstrual tension.[14 15]

Even the widely held belief that women—and especially those with symptoms of premenstrual tension—gain weight premenstrually has been challenged. In a study of 20 patients with severe premenstrual symptoms and 20 controls without symptoms Andersch *et al*[16] found that in neither group were there significant changes in water or body weight in the premenstrual period. Possibly the symptoms of premenstrual tension may be due to a redistribution of fluid—an increased flow from the intravascular to the extravascular compartment.[17] Certain tissues more than others may be sensitive to very slight alterations in their fluid environment, but we cannot yet monitor precisely the movement of water between intracellular and extracellular spaces.[16]

The continuing uncertainty over the cause of premenstrual tension is reflected in the many treatments offered. Dalton[2] claimed success with natural progesterone rather than synthetic progestogens, but the natural hormone is expensive and difficult to administer long term.[18] Taylor[7] identified a group of patients with premenstrual symptoms who had low progesterone values in the luteal phase and treated them with several progestational agents active by mouth; the most successful was dydrogesterone, which relieved many, though not all, symptoms in 70% of patients. Kerr[18] used pyridoxine in 70 patients with apparently normal progesterone or prolactin concentrations, with real benefit to between 50% and 60% of the women, especially in relieving premenstrual headache. Some success has been claimed for bromocriptine,[12] a drug which inhibits the release of prolactin, but Andersch *et al*[16] were unable to show that bromocriptine had any effect on weight or body water in their control patients or in those suffering from severe premenstrual symptoms; in the same two groups of patients a diuretic (bumetanide) was similarly ineffective.

There is no evidence, indeed, that one treatment is more effective than the others. What we need is a more precise definition of the syndrome with well-planned, carefully controlled trials of various treatments—including simple reassurance, mild sedation, or tranquillisers. Whatever else we offer these patients they are likely to appreciate an understanding and sympathetic approach to their problem, and this is where husbands, relatives, and friends as well as doctors can be of considerable help.

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Hazards of fibreoptic bronchoscopy

The reported complications of fibreoptic bronchoscopy are legion, but fortunately most of them are trivial, preventable, or readily amenable to treatment. The minor complications include epistaxis (if the conventional nasal route is used), transient laryngospasm, aphonia, vasovagal reactions, fever, minor cardiac dysrhythmias, and psychotic reactions.[1 2] Rarely, lignocaine (the drug generally used for local surface anaesthesia) produces toxic effects, particularly if precautions are not taken to limit its total dosage. General anaesthesia, too, has potential hazards. Respiratory infection, including cross-