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Systemic treatments for women with breast cancer: outcome with relation to screening for the disease

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Early detection and proper care of breast cancer are currently the best available approaches to the treatment of patients with the disease. In countries with a breast cancer screening programme, there has been a demonstrated reduction in breast cancer-related mortality. Such reduction has also been observed in Switzerland, a country in which no national programme of screening is available. Although there is no doubt that early diagnosis might have had a major role in reducing breast cancer mortality the magnitude of this effect is unknown. Research with tailored approaches on alternative imaging for early detection of breast cancer in high-risk women and on treatments offered according to proper criteria of responsiveness to therapies is warranted.

Key words: adjuvant treatments, breast cancer, screening

Increased attention has been given to breast cancer mainly as a result of the strong emotional attitude towards the breast, the shifting of paradigms related to understanding the disease, and developments of preventive, diagnostic and therapeutic modalities. Advances in each of these three latter domains have a potential impact upon freedom from disease and, ultimately, upon survival. Early diagnosis by means of mammographic screening for breast cancer has been implemented in many countries and there is definitive information on the reduction in breast cancer mortality in several nations, worldwide. Uncertainty exists, however, concerning the relative importance of prevention, screening and treatment that have contributed to this progress. Clarifying this issue might be useful for strategic decisions concerning the distribution of resources for further progress.

There is little doubt that delayed diagnosis of asymptomatic breast carcinoma (e.g. by 6–12 months) is associated with progression of breast cancer [1]. It is, therefore, reasonable to assume that any survival benefit associated with early diagnosis of breast cancer might be partially due to the better treatment outcome of less advanced disease.

In addition to early diagnosis, the features that potentially influence overall survival include the following: proper and timely surgical treatment, completion of local (and regional) treatment with radiation therapy, properly tailored systemic adjuvant therapy and, following relapse, proper systemic therapy to control symptoms and disease progression.

To assess the evidence for breast cancer mortality reduction and efficacy of systemic treatments to control disease progression, we consider separately the adjuvant setting (breast cancer confined to

the breast and the ipsilateral axillary lymph nodes; treatment aimed at avoiding overt metastatic disease) and the advanced disease setting. Adjuvant systemic therapy is given with a curative intent, while treatment for advanced disease is typically tailored to control disease progression and ameliorate symptoms of disease. There is overwhelming evidence that adjuvant systemic therapies reduce the risk of relapse and improve overall survival based on results from randomised clinical trials. Treatments such as tamoxifen {given for 5 years, mainly for women with estrogen receptor-expressing breast cancer [2], ovarian ablation [3] and polychemotherapy (given for 3–6 months) [4]} are very effective, especially for properly selected patient populations, while immune therapy [5] is not effective.

Similarly, in the advanced disease setting, several first-line systemic therapies showed an overall survival benefit in favour of one treatment or the other (novel endocrine agents, newer chemotherapy regimens versus older ones, monoclonal antibodies). The magnitude of treatment effects to prolong overall survival is unknown because several therapies given to control symptoms are also very effective for controlling disease progression. Two randomised trials have been conducted to ascertain whether first-line treatment for overt metastases should include the simultaneous use of available treatment modalities, or whether the sequential use of potentially effective treatments might be preferable to prolong time to disease progression and improve overall survival. Both trials indicated that for patients with potentially endocrine-responsive disease the sequential use of endocrine therapy followed by chemotherapy was the more efficient strategy as compared to the simultaneous use of chemotherapy and endocrine therapy as first therapeutic approach [6, 7]. These trials also showed that chemotherapy should be part of the initial therapeutic approach for patients who had a rapidly growing disease, or, obviously, those who had endocrine nonresponsive metastases. Thus,

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Table 1. Breast cancer mortality (females; standardized death rate on European population) for countries with an extended national screening programme (UK), strong national cancer society and community-based screening programmes (USA) and very limited screening programme (Switzerland, CH)

Country	All ages		35–49 years		<35 years	
	1988 mortality/ 100 000 women	% Reduction within the time period	1988 mortality/ 100 000 women	% Reduction within the time period	1988 mortality/ 100 000 women	% Reduction within the time period
UK						
1988–98	41	–20.9	32	–25.3	1.2	–31.2
1988–99		–23.1		–29.0		–22.3
USA						
1988–98	32	–17.4	24	–23.7	0.9	–19.5
Switzerland (CH)						
1988–98	37	–26.4	25	–25.4	0.7	–11.9
1988–99		–33.5		–41.0		+7.5

Per cent reduction compared with baseline for 1988. The reduction in mortality between 1988 and 1999 provides the most updated figures for the UK and Switzerland. Additional information on the time interval between 1988 and 1998 is provided for the UK, Switzerland and the USA. Although differences in case ascertainment methodologies limit direct comparisons, all three countries reflect similar reductions in breast cancer mortality over time.

it is likely that more effective therapies for women with advanced disease, especially if chosen with reasonable criteria for providing the longest progression-free survival, are presumably responsible for some of the breast cancer specific mortality reduction seen in recent years [8].

Given the demonstrated effect of systemic treatments to reduce breast cancer specific mortality, it is important to consider disease- and patient-related features to develop hypotheses regarding the choice of systemic therapy to improve breast cancer survival.

Improved imaging of breast cancer and screening programmes increased the number of small breast tumours detected [9]. Furthermore, asymptomatic breast cancer, mainly detected during screening, is considered to be biologically less aggressive [10, 11]. It might be hypothesised that proper and timely local and systemic treatments might be easier to complete for less aggressive tumours and have a larger chance of being successful in terms of acceptance, control of disease and reduced breast cancer mortality.

Some countries, such as the UK, have activated mammography screening programmes since 1988 for women aged 50–64 years [12]. Other countries, such as the USA, have also advertised a strict adherence to yearly mammograms, starting for women >40 years of age [13]. In Switzerland (CH) there is no systematic screening for breast cancer [14], but the country has a high density of physicians, especially gynaecologists, who traditionally offer care and secondary prevention for women's malignancies and advertise for yearly check-ups. Considering the last decade, the number of women in Switzerland having had a mammography in the previous 2 years was about one-third compared to USA and UK figures [15, 16]. The reduction in breast cancer mortality for women overall, and for women of premenopausal age, for whom the issue of intensity of screening and of asymptomatic detection of breast cancer is less relevant, was similar. Table 1 provides information on the breast cancer mortality national statistics for the UK, USA and Switzerland. While there may be limitations due to differences in case ascertainment methodologies, such cross-national statistics are routinely presented either together in the

same table or separately in different tables. All three countries reflect similar reductions in breast cancer mortality over time.

Evidence on the role of systemic adjuvant therapies for prolonging survival is based upon several clinical trials. Particularly for premenopausal patients, the magnitude of the effect of adjuvant therapies is large. In general, premenopausal age groups do not undergo screening mammography and increased early diagnosis might not be attributed to screening, but rather to increased awareness of women to the disease, improved imaging modalities and changes in the characteristics of the disease (e.g. increased incidence of ductal carcinoma *in situ*). Among young women, the fact that reduction in breast cancer mortality is substantial for the cohorts 35–49 years old (Table 1) may be related to the recent finding derived from several randomised trials of efficacy of adjuvant therapies according to patient age [17]. The trials confirmed that the effect of chemotherapy for premenopausal patients is substantial, but the analysis also led to the observation that very young women (i.e. <35 years old) with endocrine-responsive tumours had a statistically significantly higher risk of relapse than older premenopausal patients with such tumours despite receiving a similar cytotoxic treatment. This observation, based on 11 285 patients, contradicts the empirical assumption that more intensive chemotherapy should be given to younger women based on the dogma that higher risk of relapse represents by itself an indication for adjuvant chemotherapy [18]. A tailored adjuvant systemic treatment selected according to the biological features of the disease provides improved results. In fact, in contrast to the patients with endocrine responsive disease, the analysis of treatment outcome for patients with endocrine nonresponsive breast cancer who received chemotherapy showed similar results for younger and older premenopausal women [17].

There is no doubt that early diagnosis might play a major role in reducing breast cancer mortality. The magnitude of this effect is unknown. Despite the observed reduction in breast cancer mortality based on national statistics, there is still much room for further substantial improvement. A better understanding of responsive-

ness to treatments will help to better tailor therapies even for asymptomatic breast cancers.

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