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Brief communication

The benefit of participating to clinical research★

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Summary

We assessed the impact of participating to clinical research among 1727 women with localized breast cancer. Using as referent individuals not treated according to guidelines for systemic therapy, the adjusted hazard ratio of death was 0.70 (95% confidence interval (CI): 0.54,0.90, *p*-value: 0.006) in those treated according to current guidelines and 0.45 (95% CI: 0.27,0.73, *p*-value: 0.001) in participants to research. Participation to clinical trials results in a substantial gain in survival.

Introduction

Despite recent progress against cancer [1], participation to clinical research remains a marginal phenomenon. In 1999 in the United States, 19,000 individuals, representing 3% of all adult cancer patients, were enrolled in the National Cancer Institute-sponsored clinical trials [2]. A similar estimate is reported by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) (Dr. J. Pater, Director of Ontario-based NCIC CTG- personal communication). Population-based estimates of enrolment rates to breast cancer trials of all affiliations have usually been around 10% [3,4].

Several barriers to participation, both physician and patient-related, have been identified. As summarized by the Standing Group on Health Technology from the National Health Services [5], main obstacles to clinicians' involvement include time constraints, lack of support staff, reward or recognition, potential impact on the patient–doctor relationship, loss of professional autonomy, incompatibility of protocol with daily practice, and problems with the consent procedure. Reasons most frequently given by patients include personal preferences for a specific treatment, additional demands in terms of time, cost and procedures, problems with randomization and uncertainty, and concerns with information and consent.

Given their highly selective enrolment process, the external validity of clinical studies has been questioned. Begg et al. [6], for example, have reported an average of 23 exclusion criteria in nine multi-institutional trials of breast cancer, and percentages of ineligible patients varying between 44 and 76% in different series. Younger age and better prognosis at baseline of participants have been repeatedly demonstrated [7–11].

It is often assumed that participants to clinical trials do better than others. A recent review [12] of 24 published articles concluded that there currently are insufficient data to support such an effect, and that strategies to control for confounding variables in these evaluations were often inadequate. Any benefit could therefore be explained by selective referral. We used data from a population-based study of breast cancer conducted in Quebec, Canada, to provide additional information on this question.

Methods

The study population and sampling procedure have been described [13,14]. Briefly, women from five health regions with pathologically confirmed node-negative breast cancer diagnosed between 1988 and 1994 were sampled from the Quebec tumor registry (QTR) and hospital discharge databases. Vital status was updated five years later by linkage with the QTR, the registry of beneficiaries from the Quebec universal health insurance (RAMQ) and the mortality database. Data were collected by successive reviews of medical charts, supplemented by direct queries for information to attending physicians. Co-morbidity was estimated from the hospital discharge summary of the first admission for treatment of breast cancer using the Charlson's index [15,16]. Since patients with other malignancies were not eligible to the study, the following diagnoses were used in the calculation of the index: myocardial infarction, congestive heart failure, peripheral vascular disease,

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Table 1. Multivariate analysis of overall survival

Group of patients		Hazard ratio (95% CI)	*p*-value
Participation to clinical research	Systemic treatment consistent with guidelines		
No	No	1.0	
No	Yes	0.70 (0.54, 0.90)	0.006
Yes	–	0.45 (0.27, 0.73)	0.001

Estimates adjusted for year of diagnosis, age, co-morbidity, tumor grade, ER status, stage, and loco-regional treatment.

cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, diabetes with or without complications, hemiplegia or paraplegia, and renal disease. The St-Gallen 1992 consensus recommendations for systemic treatment of node-negative breast cancer were used as standard of care [17]. Data were analyzed by Kaplan–Meier and Cox proportional hazards analysis. The multivariate analysis compared participants to clinical trials and non-participants treated or not according to guidelines, and adjusted for year of diagnosis, age, co-morbidity, tumor grade, estrogen receptor (ER) status, stage, and loco-regional treatment.

Results

The sample included 1727 women. 153 (8.9%) had *in situ* tumors, 1055 (61.1%) stage 1, and 486 (28.1%) stage 2 disease. The majority (1574 or 91.1%) had no significant co-morbidity. Overall, 207 patients (12.0%) did enroll in an experimental protocol at the time of primary diagnosis, more than 90% of them in trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP). Among 1520 individuals who did not participate to research, 951 (62.6%) received systemic treatment consistent with guidelines. Median follow-up was 6.8 years. Three hundred and eighty patients died during this period, 143 of breast cancer specific causes.

Figure 1 displays the Kaplan–Meier estimates of overall survival for the three groups of patients. For the whole cohort, 7-year survival was 82% (95% confidence interval (CI): 80, 84%). Among participants to clinical trials, it reached 91% (95% CI: 87, 95%), whereas among non- participants, it was 82% (95% CI: 80, 85%) in women treated according to guidelines and 76% (95% CI: 72, 80%) in those treated otherwise (crude log-rank test *p*-value for the comparison of the three groups <0.00005).

Using non-participants to clinical trials who were not treated according to guidelines as referent, women who participated to research had an adjusted hazard ratio (HR) of death from any cause of 0.45 (95% CI: 0.27, 0.73, $p = 0.001$) (Table 1). Among non-participants treated according to guidelines, HR was 0.70 (95% CI: 0.54, 0.90, $p = 0.006$).

Discussion

These data support the notion that women who participate to clinical trials experience, on average, a substantial reduction in mortality from all causes. The benefit may even be greater than the one conferred by compliance with standards of care. Although we did not distinguish individuals assigned to experimental and control groups, this study had the major strength of being population-based and assessed participation to all clinical trials available to women newly diagnosed with node-negative breast cancer, not only just one single trial or a few.

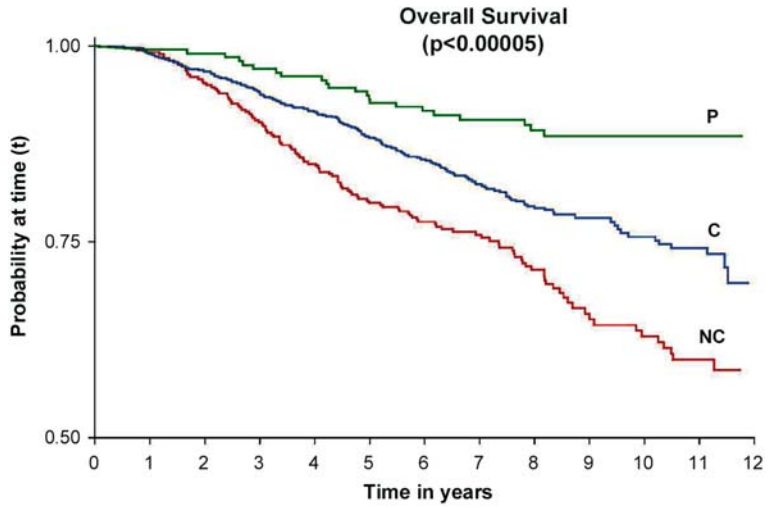

Figure 1. Kaplan–Meier estimates of overall survival for women participating to clinical trials (P) and for those not participating to clinical trials, treated according to guidelines (C) or not (NC).

Many factors could explain better outcomes of cancer patients participating to clinical research. Since the benefit observed here persisted after adjustment for case mix and key prognostic factors, selective enrolment of individuals with better prognosis is not the explanation. Participation to trials offers access to new experimental therapies with potentially superior efficacy. It involves close monitoring of patients and rigorous administration of care, even among controls. Systematic differences between providers involved or not in clinical research could also lead to better outcomes. Barriers to participation have been extensively studied. We hope that this large-scale demonstration of benefit will stimulate women, clinicians and funding agencies to find ways of increasing participation to clinical trials.

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