

# Does Adjunctive Naturopathic Care Decrease Survival Rates in Breast Cancer Patients?

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A recently published collaborative study, organized by Bastyr University and Fred Hutchinson Cancer Treatment Center, examined whether naturopathic care given adjunctively to conventional cancer treatment improves disease-free survival in breast cancer patients.<sup>1</sup> This careful study, part of a series of articles,<sup>2–8</sup> concluded that patients who chose naturopathic oncology (NO) had worse disease-free survival than a comparable cohort of patients who received usual conventional cancer care (UC) without consulting naturopaths. The authors are to be congratulated for their thorough work, and for straightforwardly publishing a negative result that raises significant questions for integrative oncology as a whole, and particularly for complex integrative systems like naturopathy that routinely incorporate multiple lifestyle and herbal or supplemental interventions.

In this matched cohort study,<sup>1</sup> patients with stages 0–III breast cancer in western Washington State, USA, were recruited. A total of 176 women who were receiving care for their cancer at any of 5 local naturopathic clinics were matched with women who were using UC. Each NO patient was matched with 2 UC patients using a regional cancer registry; the 2 cohorts had no significant differences in age, ethnicity, race, or disease characteristics. Data on treatment and outcomes were collected from the registry or from conventional or naturopathic clinic medical records, while self-reported health and sociodemographic variables were obtained by questionnaire. Patients filled out the SF-36 quality of life questionnaire annually. Disease-free survival (DFS) was the main outcome variable, and was carefully assessed using the Hudis criteria.

NO and UC patients received conventional therapy at mostly comparable rates, with 70% of each cohort undergoing guideline-compliant treatment. Estrogen-receptor positive NO patients, however, were less likely to undergo anti-estrogen therapy than UC patients. After a median follow-up time of 39.2 months, 50 women in the study had DFS-ending events, comprising 15.3% of the NO cohort and 6.8% of the UC cohort ( $P < .01$ ). Among these events, 6.3% of NO patients had second primary cancers, predominantly breast cancers, while 1.8% of UC patients experienced these ( $P < .02$ ). NO patients had contralateral breast cancers at higher rates than UC patients, although these

events did not differ significantly between groups. The NO group had worse DFS in addition to worse overall survival, with a 5-year DFS of the NO group of 80% versus 89.7% for the UC group. The more advanced patients, with Stage III disease, were the most likely to experience DFS-ending events, with a DFS of 66.1% for the NO cohort versus 93.3% for the UC patients.

While the investigators were able to match the cohorts closely on a number of variables, they did not achieve all their recruitment goals. One goal had been to develop 2 groups, one of which did not use dietary supplements and one that used supplements recommended by naturopaths. In fact, 70% of women in both groups used supplements, and types of supplements used were fairly similar. Patients in the NO group had higher incomes than the UC group, consistent with many observations of patients using complementary and integrative therapies. Patients in the NO group had lower baseline quality of life scores. In particular, their scores on the SF-36 Role Physical and Role Emotional scales were 10 points lower than the UC cohort, Social Function was 8 points lower, and Mental Health was 4 points lower. However, at the 6 month follow-up, these scores did not differ significantly from the UC group, and the NO General Health scale was 4 points higher than the UC group, a clinically significant difference. SF-36 scores from later years are not currently published, and of course are not available before the onset of the patients' breast cancer, so it is not known if the improved quality of life persisted. It should also be noted that the study is limited because it used only a small number of NO clinics, which may or may not be typical of other NO clinics in their practices or the populations they serve.

What characteristics of NO treatment could have been associated with or caused this startling differential in outcomes? The authors analyzed the low use of anti-estrogen medications, but they found that omission of these treatments

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did not predict inferior outcomes. They analyzed the most common naturopathic recommendations. These included lifestyle therapies like exercise, walking, and meditation, the latter being recommended for smaller numbers of patients. Additionally, NO treatments included acupuncture and supplements. Some of the supplements included melatonin, *Trametes versicolor* mushrooms, vitamin D, omega-3 fatty acids, curcumin, and others. Somewhat curiously, dietary modification was not one of the major therapies recommended. None of these specific treatments predicted poor outcomes. Standish et al note that women may have sought out NO care because they perceived that their conventional treatment was not going well. In fact, 18% of this cohort started NO care after completion of all their conventional treatments, when the lack of response to conventional treatment could already be evident. Data on long-term adherence to either NO or conventional treatment recommendations are lacking, although patients did visit NO practitioners an average of 5 times during their first year of NO treatment, suggesting substantial initial interest in the intervention.

In addition, the lower baseline quality of life scores might indicate that NO patients had health or lifestyle challenges that put the patients at higher risk for more aggressive disease—possibly challenges that existed before diagnosis which could have predisposed patients to recurrence and second primary cancers. In spite of the extensive and meticulous assessments performed by the authors on the 2 cohorts, there is much we do not know about these patients. There are a variety of lifestyle factors including obesity, past or current smoking or alcohol consumption, age at first pregnancy, and family history that are thought to contribute to risks of contralateral<sup>9-11</sup> or recurrent breast cancers<sup>12,13</sup> and second primary cancers,<sup>12,14,15</sup> based on varying levels of evidence. As the authors point out, there is no evidence about differences in genetic risk factors between the cohorts. And in fact, low initial quality of life in the NO cohort did not predict breast cancer outcomes. But could the low initial quality of life of the NO cohort suggest past or current struggles with obesity, smoking, alcohol, or difficulties in adapting to the breast cancer diagnosis? These unknown factors, which are not assessed by the SF-36, might in fact be behind the worse outcomes in the NO group.

Another explanation could be that this poor outcome was been mediated by refusal of conventional therapies. Kim et al,<sup>8</sup> however, did not find that refusal of anti-estrogen therapies mediated the effects they observed (a different paper on their study notes a higher rate of declining radiotherapy among the NO group than among the UC group, which is not mentioned in the final outcome paper).

But could there be other more subtle factors related to the NO treatments that adversely influenced survival? Patterns of care-seeking behavior and attitudes about use of alternative treatments are of interest in exploring this

question. Patterns of use of complementary and alternative medicine (CAM) have been analyzed in many studies, and the NO population shows some typical characteristics of CAM patients, such as a distrust of their conventional oncologists.<sup>8</sup>

Disease prognosis may influence the use of CAM practitioners by cancer patients. Among 397 patients in Norway, researchers distinguished a group who had poor prognoses at diagnosis (<20% expected 5-year survival) and a group with better prognoses (40%-60% expected 5-year survival). They found 5 levels of CAM use, some of which were used equally by the poor and better prognosis groups (eg, dietary supplements and diet change). However, the poor prognosis group used CAM practitioners significantly more often than the better prognosis group ( $P=.021$ ).<sup>16</sup> The NO group, is, of course, composed of patients who used CAM practitioners. Standish et al<sup>5</sup> however, did not find differences in initial diagnostic characteristics between the NO and UC groups, although the number of patients with grade 3 tumors was 10 percentage points higher in the NO than in the UC group. It is possible, however, that some characteristics that contribute to prognosis were not included in the study data and analysis.

Whether CAM users have any psychological factors that might predispose them to poor outcomes is a question of interest. Studies of psychological characteristics of North American CAM patients have reported findings such as both a high trait anxiety associated with using CAM for cancer, and a more intensified fear of cancer recurrence and death among CAM users without differences in depression and anxiety.<sup>17</sup> A large-scale study of U.S. colorectal cancer survivors found that among females, CAM use was associated with anxiety, recurrence fears, fatigue, anger, confusion, and emotional distress, although depression was associated with less CAM use.<sup>18</sup> On the other hand, a small study of radiotherapy patients found that CAM use was not associated with psychological disturbance, poor social support or distrust in medicine, but rather with active coping behavior.<sup>19</sup> Both NO and integrative clinicians will likely recognize in their practices patients who are burdened by anxiety and distress, as well as those who show active coping behavior. But the unresolvable question in the study by Standish et al is whether there is an excess of patients with psychological dysfunction in the NO population. This is of clinical relevance, since a recent meta-analysis involving studies of more than 280 000 patients found that depression was significantly associated with cancer recurrence, all-cause mortality and cancer-specific mortality. Anxiety was associated with recurrence and all-cause mortality but not cancer-specific mortality.<sup>20</sup>

Attitudes about CAM and health beliefs are other areas of possible differentiation between the NO and UC populations that are unexplored in the Standish et al study. Most studies of CAM use do not differentiate between

self-directed CAM use (seen in the use of supplements by the UC cohort) and use of CAM practitioners such as naturopaths—a more intensive commitment to alternative healing methods than self-directed supplement use. A recent study in Hungary, however, contrasted health beliefs of a group of patients (mixed illnesses but including many cancer patients) who were treated exclusively with conventional medicine (“biomedicine,” BM), a group of patients who used complementary medicine with biomedicine (CAM) and a group of patients who had stopped BM treatment and were treated exclusively by practitioners of traditional Chinese medicine (TCM).<sup>21</sup> In general, the attitudes of the CAM and TCM groups were similar, and differed from the BM group in several areas. CAM and TCM patients were more likely to distrust conventional biomedical tests, therapies and the practitioners that offer them. They also feel that the body is infused with an energy system (vitalism). They prefer the use of natural treatments to conventional therapy as much as possible; and tend to “psychologize” illness, or feel that illness arose from stress or other psychological difficulties.

Health beliefs that characterized the CAM and TCM patients are likely to be persistent and to antedate the breast cancer diagnoses of patients in the NO cohort. Could they have influenced behavior before patients began NO treatment, or after NO treatment was initiated? The study does not provide data on adherence or dose intensity of chemotherapy, radiotherapy or anti-estrogen therapy. With potential distrust of biomedical practitioners and therapies, NO patients may have been less adherent to these therapies, with the result that therapies may not have been optimally effective. There is little information available on whether the NO patients used other alternative practitioners before or after selecting NO treatment. Such information would have been collected from naturopathic and conventional medical records. Since fewer patients were seeing NO practitioners after their first year of treatment, and data on alternative medicine use are under-recorded in conventional medical records, information on use of other alternative practitioners must be considered incomplete. This leaves open the question of whether NO patients might have used other, potentially disadvantageous alternative practices/practitioners that were less evidence-based than those of naturopaths.

Standish et al have pioneered in leveraging their access to a large number of patients who selected adjunctive naturopathic treatment, and who were matched with cancer registry patients to execute a study that is both important and challenging. The results were not what naturopathic oncologists could have hoped for, and raise questions about the effects of a variety of natural therapies individually and in combination. But these results are not a completely convincing demonstration that naturopathic care is harmful to patients. The results raise questions

about the nature of patients who go so far as to use practitioners traditionally considered “alternative” (note that naturopaths are licensed in Washington State where the study was performed.) Their initial quality of life was low, with deficits in physical and emotional role function, social function, and mental health. The absence of information on their history of smoking, weight and weight changes, and alcohol use suggest questions about whether stress-driven past or present maladaptive behaviors could have influenced predisposition to recurrence. The possible roles of anxiety, depression, and distress in self-selecting to use alternative practitioners raise concerns. Prognostic factors that were not measured by Standish et al may have affected the course of disease in the NO cohort. And the attitudes and health beliefs of patients who use CAM in various contexts suggest possible non-adherence to conventional treatments that patients underwent, as well as possible use of disadvantageous alternative therapies that were not recorded in medical records.

While the study by Standish et al is the first matched-cohort assessment of the anticancer effects of complex natural therapies derived from Western complementary and alternative medicine, it is not the only observational study in this area. A few other studies have suggested better or neutral survival outcomes from use of integrative oncology or CAM. In a paper published by the author of this editorial, a cohort of 90 metastatic breast cancer patients receiving cancer chemotherapy at a U.S. integrative oncology clinic was found to have overall survival rates that compared favorably to those at other community clinics recorded in the literature.<sup>22</sup> A study of an integrative oncology clinic in Israel assessed survival of 189 advanced gynecological cancer patients who sought integrative care and received at least 4 integrative treatments in 6 weeks, who were considered adherent to integrative care (AIC). This group was compared with patients who sought integrative care and did not adhere (non-AIC); or who did not seek integrative care (controls). Overall 3-year survival in the AIC group was greater than that of the non-AIC group ( $P=.012$ ) or controls ( $P=.003$ ). AIC patients who used at least 3 integrative modalities had longer survival than AIC patients who used fewer than 3 modalities.<sup>23</sup> Participants in the Health Eating, Activity and Lifestyle (HEAL) study, a cohort study of stages I-III breast cancer patients, were questioned about CAM use. Participants used a variety of CAM modalities, including 13% who saw practitioners of alternative medical systems. No effect of CAM use was seen on breast-cancer specific (HR=1.04) or total mortality (HR=0.91) when compared to non-use of CAM.<sup>24</sup>

Only a randomized trial can reconcile the conflicting results resulting from the observational studies of Standish and others. Fortunately, such a trial is currently in progress at M.D. Anderson Cancer Center,<sup>25</sup> in which breast cancer

patients receiving radiation therapy are randomized to an integrative oncology intervention or control group, with disease-free survival as a main outcome. Randomization of patients who all at least consent to integrative lifestyle interventions will overcome several of the limitations of studying patients who self-select to use naturopathic practitioners as the exemplar of integrative oncology. The trial (NCT02079662) is anticipated to conclude in 2022. It is an example of well-designed trial of an intervention that originated in the US-European tradition of lifestyle interventions. Its completion will begin filling in the evidence base for such therapies, which is still relatively narrow in comparison to the many well-designed randomized trials of herbal formulas in Asia that have recently begun to be carried out and published.<sup>26</sup>

Based on the results of the Standish et al publication, and on our analysis of factors that may underlie the negative results it reports, naturopathic practitioners should monitor scientific literature and be vigilant for any reports of adverse interactions between natural and conventional therapies. They also need to be sensitive to their patients' emotional states, quality of life and any trust issues that may be disturbing their patients. They should investigate and attempt to remediate past and present risky lifestyle habits. And they should advocate for the appropriate use and timely implementation of conventional therapies in a sensitive but vigorous manner when such therapies are clinically supported. Supporting appropriate use of conventional treatment is a task that is becoming ever more difficult with the proliferation of organizations and publications that are currently urging patients to refuse chemotherapy and other treatments, but it is of obvious importance.

Some randomized studies of specific interventions, as well as other observational studies, suggest that integrative therapies have great potential to improve cancer patients' quality of life, disease outcomes and survival. Well-designed randomized studies of comprehensive, multi-faceted integrative programs, as challenging as they may be, are truly the only way forward in determining how the potentials of integrative therapies can be implemented clinically to benefit current and future cancer patients. The carefully designed and implemented study of Standish et al raises questions and concerns as to whether a NO approach is sufficiently different from integrative approaches to explain outcomes that differ markedly from the positive results of trials on integrative therapies. The approximate 10% deficit in 5-year disease-free survival of the NO cohort is a worrisome statistic. Thus, it is incumbent on the naturopathic oncology, integrative oncology, and cancer research communities to explore and better grasp whether these study results are a unique departure from existing and expected findings of the benefits of integrative therapies, or a clinically troubling outcome that must be addressed with modifications of naturopathic interventions.

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