Survey of Lifestyle, Past Medical History and Complementary and Alternative Medicine Use Among Adult Patients Participating in the National Cancer Institute’s Exceptional Responders Initiative

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ABSTRACT
Introduction: The Exceptional Responders Initiative (ERI) at the National Cancer Institute attempts to correlate unusually good outcomes in patients with cancer with genetic targets in tumors and the therapies the patients received. It is not known if other factors might contribute to exceptional responses or outcomes. We explored aspects of the medical history, lifestyle changes, complementary and alternative medicine (CAM) use and communication between health care practitioners and patients who experienced an exceptional response following cancer treatment.

Methods: All subjects whose case was submitted to the ERI were eligible to participate in the survey. A 121-question survey questionnaire was developed to assess aspects of the subject’s past medical history, lifestyle (e.g., diet, exercise, spirituality) and use of CAM.

Results: Thirty subjects completed and returned the questionnaire from approximately 88 patients invited to participate (approximate response rate = 34%). Approximately 68% were female and 32% were male. Fifty percent of subjects changed their diet after their cancer diagnosis. Eighteen patients (60%) reported using a CAM therapy (not including oral vitamins/minerals or spiritual practices) during their Exceptional Response (ER).

Conclusion: Multiple factors, including features of the tumor itself, the patient, or the environment, could affect tumor response or patient survival, either solely or in combination with the treatments received. Many patients use other medications, change their diet or physical activity or use CAM interventions after their cancer diagnosis. Investigators attempting to understand the exceptional response phenomenon should acquire rich data sets of their subjects that include information about these factors.

Background
The Exceptional Responders Initiative (ERI) at the National Cancer Institute (NCI) attempts to understand why certain patients with cancer have unusually good outcomes by extensively studying the genetic make-up of the cancer cells of such patients [1]. Ultimately, it is hoped that this process will lead to an improved understanding of tumor and treatment interactions so that predictive models can be developed to better guide the development of experimental therapies or the use of current approved therapies.

Some previously documented instances of exceptional outcomes appear to be clearly, and likely exclusively, due to the fortuitous confluence of a patient who receives a targeted therapy and whose tumor had a sensitizing mutation for the genetic target of the therapy [2, 3]. However, it is not known if such situations are the only mechanism through which exceptional responses or exceptional outcomes occur. Other factors related to the patient, or the environment, may play a role in these exceptional responses.

Many patients make significant lifestyle changes after receiving a cancer diagnosis [4–6]. Some lifestyle modifications have been
associated with improved survival. For example, epidemiological studies have found associations between the level of physical activity and survival in patients with breast [7], colon [7] and prostate cancer [8]. However, if there is a causal relationship between these factors, the mechanisms of action have yet to be identified.

A survey using data from the 2002, 2007 and 2012 National Health Interview Survey (NHIS) estimated 35.3% of persons with a cancer diagnosis used complementary and alternative (CAM) approaches in the past 12 months [9]. Other studies have found greater use among patients with advanced stages of disease [10]. This use is often not disclosed to conventional healthcare practitioners (CHCPs) caring for these patients [11].

We sought to explore aspects of the medical history, lifestyle changes, CAM use and communication between health care practitioners and patients who experienced an exceptional response following cancer treatment.

Methods

Methods for submitting cases to the ERI have been published [1,12]. All subjects whose case was submitted to the ERI were eligible to participate in the survey, regardless of whether the subject’s anti-tumor response met the criteria for an exceptional response (as defined in the ERI protocol). The ERI protocol defined ER patients as those for whom a complete or partial response was expected in less than 10% of similarly treated patients or whose duration of response was exceptional, e.g., lasted at least three times the published median duration [1].

The survey questionnaire titled “Lifestyle and Past Medical History Survey of Adult Patients Participating in the NCI’s Exceptional Responders Initiative” was based on the NHIS 2012 CAM Subset [13] with added questions about other aspects of the subject’s past medical history and lifestyle (e.g., diet and exercise). This 121-question questionnaire also contains questions about what CAM approaches were used, when and why they were used, the subject’s opinions of effectiveness of these approaches and whether they discussed the use of these approaches with their conventional healthcare practitioners (CHCPs). CAM therapies are a diverse group of interventions that are not an integral part of conventional Western medicine and include herbal medicines, nutritional supplements, diet modifications as well as mind-body approaches and others [14]. Some CAM definitions include the use of vitamin/mineral supplements and spiritual practices [15]. In this analysis, CAM is defined as the use of alternative medical systems (e.g., homeopathy, naturopathy), herbal therapies, mind-body interventions (e.g., meditation, relaxation therapy), energy/biofield therapies (e.g., healing touch, Reiki), manual therapies (e.g., massage, chiropractic), and other unconventional treatments (e.g., intravenous vitamin C, Rife machine).

The study protocol was reviewed and approved by the NCI Central Institutional Review Board as well as the ethics committees of the participating accrual sites. Subject recruitment took place from May 2017 through September 2019 and occurred in 2 phases. In the first phase, subjects were offered an opportunity to participate in the study when they attended oncology clinic at the various accrual sites. A signed consent form was required for participation in the study. Subjects who agreed to participate were mailed the survey questionnaire and a $25 thank you gift card. Pertinent information from each subject’s case history (e.g., the dates for the exceptional response period) was inserted into the copy of the individualized questionnaire mailed to subjects. Accrual sites were paid $25 for every patient to whom they offered participation in the study. Based on the information provided by these sites, 23 subjects from 14 sites were approached to participate in the first phase of the study. Twenty-one subjects consented to participate in the study, while 2 declined. Of those that consented, 16 returned the survey questionnaire. (Fig 1)

Due to slow accrual, a protocol amendment was implemented that allowed participating sites to send study packets (letter to subjects requesting their participation, consent form and questionnaire) to all living subjects recruited to the ERI protocol. Subjects who consented to participate in phase one were excluded from phase two. Study sites received a compensation of $50 for each packet mailed to subjects during the second phase of recruitment.

In the second phase of recruitment, 16 sites agreed to participate for a total of 84 eligible subjects. Of these, 14 sites confirmed mailing study packets to 65 subjects while 2 sites did not confirm mailing the study packets to their 19 eligible ERI subjects. Fourteen completed questionnaires were sent back to the study coordinator during the second phase of recruitment for a total of 30 completed questionnaires received during the 2 phases of recruitment.

Statistics

Descriptive statistics were calculated to summarize the responses. Categorical variables were summarized as frequencies and relative frequencies. Continuous variables were summarized as means or medians along with measures of dispersion such as standard deviations, quartiles, and ranges, as appropriate. Associations between categorical variables were presented in contingency tables along with measures of association as appropriate depending on number of variables and number of categories of response per variable. Associations between categorical and continuous variables are presented as descriptive statistics for the continuous variable by response for the categorical variable. Associations between continuous variables (e.g., CAM use, age, and income) were evaluated using Spearman correlation [16-18].

For the primary endpoints listed below, descriptive statistics are accompanied by 95% confidence intervals for point estimates (e.g., 95% Wilson’s confidence interval) [19,20] or two-sided 0.05 level statistical tests for measures of association (e.g., Wilcoxon rank sum test) [21,22].

Primary endpoints: a) Percentage of ER subjects who used a CAM intervention before or during the period of their exceptional response. b)
Association between CAM use and various demographic parameters (e.g., gender, age, income status). c) Frequency of use of specific subcategories of CAM (e.g., dietary supplements) by ER subjects. d) Frequency of use of specific CAM products/interventions (e.g., fish oil, or special diet) by ER subjects. e) Frequency of dietary change after the cancer diagnosis f) Frequency of increase in weekly minutes of physical activity after the cancer diagnosis

Results

Demographics (Table 1)

Thirty subjects completed and returned the survey questionnaire from approximately 88 patients invited to participate (approximate response rate = 34%). Subjects ranged in age from 45 to 86 years (mean age = 68.7 years and median age = 70.5 years) (n = 27, 2 subjects with missing data, and one subject who wrote age = 4 years). Approximately 68% were female and 32% were male. Caucasians constituted 93% of the study cohort. All subjects lived in the United States with most living in the Midwest (68%). Seventeen subjects had a bachelor’s or higher degree, and thirteen [13] subjects had a high school diploma as their highest academic achievement.

The most common cancer types in the subjects were colorectal(6), breast(4), lung(4), esophagus/gastric(3), pancreas(3), mesothelioma(2), and ovary(2). Other cancer types included liver, head and neck, melanoma, renal, bladder, and fallopian tube.

Diet and Physical Activity (Table 1)

Approximately 93% of the subjects had a western diet prior to their cancer diagnosis. Fifty percent [0.50 (95%CI 0.51-0.69) changed their diet after their cancer diagnosis. The changes included eating less carbohydrates (87%), less meat (67%) and more fruit and vegetables (93%). One subject each started vegetarian, vegan, ketogenic and alkaline diets during their exceptional response period.

Before their cancer diagnosis 10% of the subjects had a sedentary lifestyle, while 36.7% were active but not regularly exercising. Forty percent of the subjects changed their level of physical activity after their cancer diagnosis. Interestingly, of those subjects who changed their level of activity, 16.7% stopped exercising, while 25%, 33.3% and 25% of the subjects started low, medium, or high exercise respectively. The proportion of subjects who increased weekly minutes of physical activity (i.e., moved up one or more categories, see Table 2 for categories) after cancer diagnosis was 0.33 (95%CI 0.17-0.53)

Among the specific types of exercise engaged in by subjects were: yoga(9), Pilates(2), and tai chi (2. (Table 3, Table 4)

When asked about their opinion of what role diet or physical activity played in their exceptional response, 2 (6.7%) subjects indicated that diet or physical activity was fully responsible, 13 (43.3%) indicated that diet or physical activity was partially responsible, while 15 (50%) indicated that diet or physical activity was not significantly responsible for their exceptional response.

Use of CAM (Table 3 and Table 4)

The survey questionnaire asked whether subjects used various specific CAM approaches and if so when (i.e., more than 12 months prior to the ER period, <12 months prior to the ER period, during the ER period, after the ER period). The results below focus on the reports of the CAM approaches used by the respondents during their ER period. Eighteen patients (60%, 0.60, 95% CI 0.41-0.77) reported using a CAM product, practice, or therapy (not including oral vitamins/minerals or spiritual practices) during their ER. These CAM users generally used multiple CAM approaches (median = 2, mean = 4.8). The range of CAM use was 1 to 18. The association between CAM use and age was significant with a negative correlation; Spearman= -0.5455, p = 0.0026 (i.e., CAM use
Dietary Supplements and Diet Therapies

Eighteen patients (60%, 0.60, 95% CI 0.41-0.77) reported using dietary supplements. Half of the subjects (n = 15, 50%) used oral vitamin or mineral supplements during the ER period. Eleven subjects (36.7%) used other dietary supplements (Not shown in Table 3). Fish oil was the most frequently used dietary supplement (n = 8; 0.27 [95% CI 0.12-0.46]). Other commonly used supplements were: probiotics/prebiotics (3), curcumin(3), coenzyme Q10(3) and melatonin(3).

Six subjects used dietary supplements or therapies for cancer or an associated condition, while three and four subjects respectively used them for symptom or treatment side effect management and an increased chance of survival.

Energy/Biofield, and Mind-body Therapies

One subject each received Reiki therapy, Healing Touch and Therapeutic Touch treatments. Meditation was practiced by three subjects, two practiced guided imagery and one progressive relaxation.

Manual Therapies

Massage therapy was the most common manual therapy used during the ER period (n = 10). Four subjects used chiropractic or osteopathic manipulation during their ER. Two subjects used chiropractic or osteopathic manipulation with the intent of treating the cancer, a condition due to the cancer itself or its treatment.

Alternative Medical Systems

Five subjects used homeopathic treatment during the ER period and 4 of them visited a homeopathic practitioner. Two subjects sought treatment by a naturopathic physician during their ER. Five subjects used either homeopathy or naturopathic medicine to aid the treatment by a naturopathic physician during their ER. Five subjects used other dietary supplements (Not shown in table 3). Fish oil was the most commonly used dietary supplement (n = 8; 0.27 [95% CI 0.12-0.46]). Other commonly used supplements were: probiotics/prebiotics (3), curcumin(3), coenzyme Q10(3) and melatonin(3).

Table 2

| Diet - Prior to cancer diagnosis * | Total
|-----------------------------------|------|
| Normal Western diet               | 28 (93.3%) |
| Mediterranean diet                | 2 (6.7%)  |
| Other                             | 1 (3.3%)  |

| Diet - Diet change since diagnosis | Total
|-----------------------------------|------|
| Less refined carbohydrate         | 13 (86.7%) |
| Less meat                         | 10 (66.7%) |
| Increased fruits and vegetables    | 14 (93.3%) |
| Vegan                             | 1 (6.7%)  |
| Lacto-ovo vegetarian              | 1 (6.7%)  |
| High protein, low carbohydrate    | 2 (13.3%) |

| Physical Activity - Prior to cancer diagnosis | Total
|------------------------------------------------|------|
| Sedentary                                   | 3 (10%) |
| Active; not regularly exercising            | 11 (36.7%) |
| Physical job; not regularly exercising      | 2 (6.7%)  |
| Low exercise (up to 60mins/week)            | 2 (6.7%)  |
| Medium exercise (61-150mins/week)           | 4 (13.3%) |
| High exercise (>150mins/week)               | 5 (16.7%) |

| Physical Activity - Activity change | Total
|------------------------------------|------|
| Stopped exercising                 | 2 (16.7%) |
| Started an active job              | 1 (8.3%)  |
| Started low exercise (up to 60mins/week) | 3 (25%)  |
| Started medium exercise (61-150mins/week) | 4 (33.3%) |
| Started high exercise (>150 mins/week) | 3 (25%)  |

Table 3

| Complementary and Alternative Medicine Use. | Total Use | < 12 months Prior to ER | During ER |
|--------------------------------------------|-----------|-------------------------|-----------|
| Alternative Medical Systems                |           |                         |           |
| Naturopathic Physician treatment           | 2         | 1                       | 2         |
| Homeopathic treatment                      | 7         | 2                       | 5         |
| Practitioner of Homeopathic treatment      | 4         | 1                       | 4         |
| Nutritional Therapies                      |           |                         |           |
| Multivitamin or multimineral               | 23        | 2                       | 13        |
| Other vitamins (A, B, C, D, E, H, K)       | 15        | 1                       | 12        |
| Other minerals (Ca, Mg, Fe, Cr, Zn, Se, K) | 20        | 1                       | 14        |
| Supplements                                |           |                         |           |
| Acai                                       | 1         | 0                       | 1         |
| L-Arginine                                 | 1         | 0                       | 1         |
| Astragalus                                  | 1         | 0                       | 1         |
| Chondroitin                                | 4         | 1                       | 2         |
| Co-enzyme Q10                              | 3         | 0                       | 3         |
| Curcumin                                   | 4         | 1                       | 3         |
| Digestive enzymes                          | 3         | 1                       | 2         |
| Echinacea                                  | 2         | 0                       | 0         |
| Fish oil or Omega-3 Fatty acids            | 14        | 1                       | 8         |
| Garlic                                     | 1         | 0                       | 0         |
| Ginkgo biloba                              | 2         | 0                       | 0         |
| Ginseng                                    | 1         | 0                       | 0         |
| Glucosamine                                | 4         | 1                       | 2         |
| Melatonin                                  | 6         | 0                       | 3         |
| Mushroom products                          | 2         | 0                       | 2         |
| Milk thistle                               | 1         | 0                       | 0         |
| Probiotics or prebiotics                   | 9         | 2                       | 3         |
| Supplements (cont.)                        |           |                         |           |
| Combination herb mixture                   | 3         | 0                       | 3         |
| Exercise Therapies (ET)                    |           |                         |           |
| Yoga                                       | 9         | 2                       | 7         |
| Tai Chi                                    | 2         | 0                       | 1         |
| Pilates                                    | 2         | 0                       | 2         |
| Diet Intervention                          |           |                         |           |
| Vegetarian                                 | 2         | 0                       | 1         |
| Atkins                                     | 1         | 0                       | 0         |
| Ketogenic                                  | 1         | 0                       | 1         |
| Alkaline                                   | 1         | 0                       | 1         |
| Other Interventions                        |           |                         |           |
| Intravenous vitamin C                      | 1         | 0                       | 1         |
| Chelation therapy                          | 1         | 0                       | 1         |
| Personal cocktail                          | 1         | 0                       | 1         |
| Other CAMs*                                | 3         | 0                       | 3         |
| Spiritual Practices                        |           |                         |           |
| Personal prayer                            | 18        | 7                       | 16        |
| Intercessory prayer                        | 22        | 5                       | 20        |
| Other spiritual Intervention               | 7         | 3                       | 6         |
| Manual Therapies                           |           |                         |           |
| Chiropractic/Osteopathic manipulation      | 7         | 1                       | 4         |
| Massage therapy                            | 10        | 0                       | 10        |
| Acupuncture                                | 6         | 1                       | 4         |
| Mind-body Therapies                        |           |                         |           |
| Meditation                                 | 5         | 1                       | 3         |
| Guided imagery                             | 3         | 0                       | 2         |
| Progressive relaxation                     | 2         | 0                       | 1         |
| Energy/Biofield Therapy                    |           |                         |           |
| Total Use                                  |           |                         |           |
| < 12 months Prior to ER                    |           |                         |           |
| During ER                                  |           |                         |           |
| Reiki                                      | 5         | 0                       | 1         |
| Healing touch                              | 3         | 0                       | 1         |
| Therapeutic touch                          | 1         | 0                       | 1         |
| Other energy therapy                       | 1         | 0                       | 1         |

ER = Exceptional response.
*Huan Qin Tang, Reflexology and True Rife.
# Personal Cocktail - Drugs generally prescribed for other indications which a patient uses to treat their cancer. [62] This subject did not provide details of drug components of this cocktail.

The percentages were determined from the number of subjects indicating an activity change (i.e. n = 12).

decreased with age), while the association between CAM use and income was not significant; Spearman = 0.0566, p = 0.8072. The association between CAM use and gender was significant; Wilcoxon rank sum test W=129.5, p=0.0266.

* One subject selected two responses. # Percentages add to greater than 100 due to subjects choosing multiple response options.
† The percentages were determined from the number of subjects indicating an activity change (i.e. n = 12).
Table 4
Summary of Survey Subjects.

| Subject No. | Cancer Type | Treatment Associated with Exceptional Response | Response (Duration) | ERI Criteria Met? | Medications taken during ERI period | Diet Change | Exercise Change | Spiritual practices/therapies | Vitamins/Minerals | Mind-Body and Energy Therapies | Other CAM Use and Type |
|-------------|-------------|-------------------------------------------------|---------------------|------------------|-------------------------------------|------------|-----------------|---------------------------|-------------------|-----------------------------|----------------------|
| 0454        | Ovarian carcinoma (Adenocarcinoma, Endometrioid type), stage IV | Paclitaxel, Carboplatin, Temsirolimus (Clinical Trial) | Complete Response 70+ months | Yes | Citalopram, Glimepiride, Enalapril, Amlodipine, Atorvastatin, Aspirin, Levothyroxine | Yes (More fruit/vegetables, less refined carbohydrates) | No | Yes | None | None |
| 0422        | Small cell Lung cancer with bulky mediastinal disease and bone lesion | Cisplatin, Etoposide | Complete Response 24 months | No | Sertraline, Clonazepam | Yes (Less refined carbohydrates, more fruits/vegetables) | Yes | Yes | Vitamin D, Magnesium | Meditation, Yoga |
| 0010        | Adenocarcinoma of the Colon (cecum), stage IVB | Bevacizumab, Irinotecan | Complete Response 12+ months | Yes | Irbesartan, Metoprolol, Zetia | No | No | Yes | None | None | None |
| 0458        | Metastatic mesothelioma with local pleural recurrence | Carboplatin, Pemetrexed | Complete Response 36+ months | No | Acetaminophen, Tiotropium, Fluticasone propionate nasal spray, Prochlorperazine, Diphenhydramine, Lisinopril, Metoprolol, Atorvastatin, Aspirin, Clopidogrel, Dexamethasone, Furosemide, Potassium, Levothyroxine | No | No | Yes | Multivitamin/Multimineral, Vitamin D, B, Calcium | None | Ginseng |
| 0132        | Adenocarcinoma of the Lung, stage IV | Docetaxel, Bevacizumab | Complete Response 88+ months | Yes | Mupirocin, Carzepin | No | No | Yes | None | None | None |
| 0226        | Adenocarcinoma of the Lung, stage IV | Carboplatin, Pemetrexed | Partial Response 48+ months | Yes | None Listed | Yes (Vegetarian) | Yes | No | Multivitamin/Multimineral, Vitamin D3, Calcium, Iron | Guided imagery, progressive relaxation, meditation, Tai Chi, Reiki, massage | Homeopathy, melatonin, Huan Qin Tang |
| 0060        | Adenocarcinoma of the Colon, stage IV | 5-FU, Oxaliplatin, Leucovorin calcium, Bevacizumab | Complete Response 122+ months | Yes | None Listed | No | No | Yes | None | None | None |
| 0376        | Adenocarcinoma of the Esophagus, stage IV | Capecitabine, Cisplatin, Trastuzumab | Complete Response 51+ months | Yes | Acetaminophen + diphenhydramine, Gabapentin, Sertraline, Lisinopril, Omeprazole | No | Yes | Yes | Multivitamin/Multimineral, Vitamin B6, C, E, Iron, Magnesium, Potassium | None | Fish oil |
| 0457        | Adenocarcinoma of the Colon (sigmoid), stage IV | 5-FU, Oxaliplatin, Leucovorin calcium, | Complete Response 39+ months | Yes | Levothyroxine sodium | Yes (Less refined carbohydrates, less refined carbohydrates) | Yes | No | Multivitamin/Multimineral, Vitamin B, D, Calcium | None | None | (continued on next page)
| Subject No. | Cancer Type | Treatment Associated with Exceptional Response | Response (Duration) | ERI Criteria Met? | Associated with Exceptional Response | Diet Change | Exercise Change | Spiritual practices/therapies | Vitamins/Minerals | Mind-Body and Energy Therapies | Other CAM Use and Type |
|------------|-------------|-------------------------------------------------|---------------------|------------------|-------------------------------------|-------------|----------------|-------------------------------|-----------------|-----------------------------|----------------------|
| 0312       | Breast cancer, triple negative, stage IV        | Bevacizumab, Irinotecan, Paclitaxel, Capecitabine | Complete Response 108+ months | No               | Pregabalin, Carvedilol, Metolazone, Aspirin, Furosemide, Potassium | meat, more fruits/vegetables | Yes           | Yes                          | Multivitamin/Multimineral, Vitamin B complex, C, Potassium | None            | None                        | Fish oil, CoQ10       |
| 0500       | Hepatocellular carcinoma, stage IV              | Durvalumab (Clinical Trial)            | Partial Response 19+ months | Yes              | Rivaroxaban, Diltiazem HCl         | No          | No            | Yes                          | None            | None                        | None                |
| 0501       | Carcinoma of the Colon, stage IV               | Nivolumab, Varilimumab (Clinical Trial) | Partial Response 7+ months | Yes              | Losartan, Tamulosin               | No          | No            | Yes                          | None            | None                        | None                |
| 0347       | Carcinoma of the Pancreas, stage IV            | Everolimus (Clinical Trial)            | Partial Response 48+ months | Yes              | Oxycodone, Venlafaxine, Glipizide, Metformin, Sandostatin, Carvedilol, Hydroxyzine, Lisinopril, Fenofibrate, Quetiapine fumarate, Clonazepam, Furosemide, Spirinolactone, Naloxegol, Cyclohexazaine | Yes (Less refined carbohydrates, less meat, more fruits/vegetables) | No         | No            | No                           | Multivitamin/Multimineral, Magnesium, Iron | Massage | None                        |
| 0152       | Adenocarcinoma of the Lung, stage IV           | Paclitaxel, Carboplatin, Cetuximab (Clinical Trial) | Partial Response 36+ months | Yes              | Hydrocodone + acetaminophen, Minocycline, Tobramycin-dexamethasone, Warfarin, Gabapentin, Metoprolol, Aspirin, Acyclovir, Polyethylene glycol 3350, Omeprazole, Zolpidem | No          | No            | Yes                          | Multivitamin/Multimineral, Vitamin C, Calcium, Magnesium, Iron | Healing Touch | Chiropractic Medicine, Acupuncture, Fish oil, Mushroom product (Maitake) |
| 0442       | Bladder cancer, small cell type, stage IV      | Paclitaxel, Carboplatin (Clinical Trial) | Complete Response 78+ months | Yes              | Gabapentin, Amytriptylne, Lisinopril | No          | No            | Yes                          | None            | None                        | None                |
| 0165       | Breast cancer, stage IV with leptomeningeal disease | Radiation therapy, Tamoxifen, Methotrexate | Complete Response 24 months | No                | Morphone Sulfate ER, Oxycodone + acetaminophen, Nitrofurantoin mcr, Gabapentin, Amytriptylne, Prochloperazaine, Benzomazate, Valacyclovir, Oxbytynin, Probiotics, Omeprazole | Yes (Ketogenic diet) | Yes           | No                           | Multivitamin/Multimineral, Vitamin B, C, D, Calcium | Reiki, guided imagery, Yoga, Massage, | Chiropractic medicine, Naturopathic medicine, Homespasmy, Acupuncture, IV Vitamin C, Chelation, Digestive enzyme, Garlic, Fish oil, probiotics, Combination herb, True Rife |
| 0108       | Melanoma, Stage IV metastatic (cheek and axillary lesions with pulmonary nodules) | Dacarbazine (Clinical Trial)            | Complete Response 59+ months | No                | Latanoprost ophthalmic solution, Timolol maleate | No          | No            | No                           | None            | None                        | None                |
Table 4 (continued)

| Subject No. | Cancer Type | Treatment Associated with Exceptional Response | Response (Duration) | ERI Criteria Met? | Medications taken during ER period | Diet Change | Exercise Change | Spiritual practices/therapies | Vitamin/Minerals | Mind-Body and Energy Therapies | Other CAM Use and Type |
|-------------|-------------|-----------------------------------------------|---------------------|------------------|------------------------------------|-------------|-----------------|------------------------------|-----------------|-----------------------------|----------------------|
| 0413        | Esophageal adenocarcinoma, Stage IIIA local recurrence | FOLFIRI Partial Response 41+ months | No | Tiotropium, Fluticasone propionate + salmeterol xinafoate, Warfarin, Loperamide, Digoxin, Esomeprazole magnesium, Levothyroxine, Dutasteride, Tamsulosin | No | Yes | Yes | Multivitamin/Multimineral | None | None | Probiotics |
| 0342        | Gastric carcinoma, stage IV (with liver metastasis) | FOLFOX Partial Response 15 months Complete Response 22+ months | No | Metoprolol, Doxazosin | No | No | Yes | None | None | None | None |
| 0158        | Clear Cell Adenocarcinoma of Ovary | Paclitaxel, Cisplatin, Bevacizumab Complete Response 47+ months | No | Latanoprost ophthalmic solution, Timolol maleate | Yes (Less meat, more fruits/vegetables) | Yes | Yes | Multivitamin/Multimineral, Vitamin B, C, E, Calcium, Magnesium | Yoga | Chiropractic medicine, Homeopathy, Acupuncture, Fish oil, CoQ10, Curcumin, Chondroitin, Glucosamine, Melatonin |
| 0123        | Right Fallopian tube carcinoma, stage IIIC | Carboplatin, Paclitaxel (Clinical Trial) Complete Response 41+ months | No | Phenytoin | Yes (Less refined carbohydrates, less meat, more fruits/vegetables) | Yes | Yes | Multivitamin/Multimineral, Calcium | Massage | Fish oil, Melatonin, CoQ10, Acupuncture, |
| 0508        | Breast carcinoma, stage IV | Trastuzumab Complete Response 130+ months | Yes | Acetaminophen + Aspirin + Caffeine, Tramadol, Amoxicillin, Rizatriptan benzamate, Valacyclovir, Chonazepam, Phenetermine | Yes (Less refined carbohydrates) | No | Yes | Multivitamin/Multimineral, Vitamin B, C, D, Calcium, Iron | Yoga, Pilates, Massage | Fish oil, Melatonin, CoQ10, Acupuncture, |
| 0514        | Breast cancer, stage IV | Trastuzumab, Pertuzumab, oophorectomy, anastrazole Gemzar, Taxotere (Clinical Trial) Partial Response 31+ months | No | Cetirizine, Fenofibrate | Yes (Organic food, avoid food with hormone) | Yes | Yes | Calcium, Iron | Therapeutic touch, Yoga, Massage | Homesopathy |
| 0074        | Pancreatic Adenocarcinoma, Stage III | Carboplatin, Paclitaxel (Clinical Trial) Complete Response 48+ months | No | None Listed | No | No | Yes | None | None | None | None |
| 0098        | Peritoneal mesothelioma, metastatic | Imatinib Complete Response 168+ months | No | Mometasone furoate, Montelukast sodium, Amoxicillin, Azithromycin (z-pak), Ciprofloxacin, Metronizadole, Vancomycin, Fenofibrate, Probiotics, Celecoxib, Budesonide | Yes (Less refined carbohydrates, High fat/protein content, low carbohydrates, Paleo diet, gluten free diet) | Yes | Yes | Multivitamin/Multimineral | Yoga, Pilates, Massage | Chiropractic medicine, Naturopathy, Homeopathy, Fish oil, Probiotic, glucosamine, Digestive enzymes, Curcumin, Astagalus, Acai, Chondroitin, Mushroom product, Homocysteine Supreme Adrenal, 7 Keto DHEA |
| 0389        | Pancreatic cancer, metastatic (9cm mass in head of pancreas with | FOLFOX Complete Response 31+ months | No | Oxycodone, Docusate sodium | Yes (Less refined carbohydrates, less | Yes | No | None | Massage | (continued on next page)
| Subject No. | Cancer Type | Treatment Associated with Exceptional Response | Response (Duration) | ERI Criteria Met? | Medications taken during ER period | Diet Change | Exercise Change | Spiritual practices/therapies | Vitamins/Minerals | Mind-Body and Energy Therapies | Other CAM Use and Type |
|-------------|-------------|-------------------------------------------------|---------------------|------------------|-----------------------------------|-------------|----------------|-------------------------------|-----------------|--------------------------|----------------------|
| 0248        | Colon cancer, Stage IVB | XELOX, Bevacizumab (Clinical Trial) | Complete Response 24+ months | No | Oxycodone | No | No | No | None | None | None |
| 0390        | Squamous cell carcinoma of Head and Neck, stage IVA | Bevacizumab, Cisplatin, Docetaxel (Clinical Trial) | Complete Response 48+ months | Yes | Tramadol, Trazodone, Levothyroxine | Yes | Yes | No | None | Yoga, Meditation | Homoeopathy, Curcumin, Alkaline water, |
| 0398        | Rectal Cancer, stage IV | Capecitabine | Partial Response 72+ months | No | | No | No | Yes | None | None | None |
| 0438        | Renal cell carcinoma, clear type, stage IV | Sunitinib | Complete Response 122+ months | No | Insulin glargine, Glipizide, Carvedilol, Dorzolamide, Bimatoprost Ophthalmic, Simvastatin, Aspirin, Levothyroxine, Tamsulosin | No | No | No | None | Massage, Fish oil, Reliv |

5-FU: 5-Fluorouracil.
FOLFIRI: FOL = Leucovorin Calcium (Folinic Acid); F = Fluorouracil; IRI = Irinotecan Hydrochloride.
FOLFOX: FOL = Leucovorin Calcium (Folinic Acid); F = Fluorouracil; OX = Oxaliplatin.
XELOX: XEL = Capecitabine (Xeloda); OX = Oxaliplatin.
Reliv: Brand name for a series of nutritional products and dietary supplements.
7 Keto DHEA: 7-keto-dehydroepiandrosterone.
management of their cancer or a condition due to the cancer or treatment of the cancer, four used it to manage a symptom or treatment side effect and three subjects used it for an increased chance of survival.

**Herbal Therapies**

Seven subjects reported using herbal products. Those most frequently used during the ER period were curcumin(3) and combination herb mixtures(4). One subject identified the combination herb mixture they used as Huan Qing Tang.

**Other Therapies**

One patient used both a True Rife machine and intravenous vitamin C during the ER period. This patient also used chelation therapy, fascial stretch therapy and Bowen therapy, though it is not clear if these were used during the ER period.

**Opinions Regarding Impact of CAM Use on ER**

When the subjects were asked their opinion of what role CAM therapies played in their exceptional response, three subjects indicated that it was fully responsible, four said it was partially responsible, while four said it was not significantly responsible. Nineteen subjects did not respond to this question.

**Discussing CAM with CHCPs**

Nineteen subjects responded that they did not use CAM and thus did not discuss CAM with their CHCP, while 8 subjects indicated they did use CAM and discussed this use with at least one of their CHCPs. Three subjects did not answer this question, including the subject who reported using a True Rife machine and intravenous vitamin C during their ER period. Elsewhere in the survey, that subject indicated they did not discuss their use of these interventions with their CHCPs because the CHCPs did not ask, there was insufficient time in the medical encounters, and they were concerned about receiving a negative reaction from the CHCP.

Five subjects confirmed that the information/guidance given by their CHCPs about CAM was helpful, one subject said it was somewhat helpful and another subject did not find the information helpful. Five subjects felt the overall quality of the dialogue with their CHCP about their use or interest in CAM was very good. One subject each indicated that the quality of dialogue was satisfactory, neither good nor bad, or disappointing/very bad. Subjects learned about CAM therapies from family, friends/co-workers, internet, books, health food store, and health care practitioners (data not shown).

**Spirituality**

Sixteen, twenty and 6 subjects used personal prayer, intercessory prayer, and other spiritual practices respectively during the ER period. Twenty-two subjects used a spiritual practice with the intent of curing or managing the cancer, four used it to manage a symptom or treatment side effect and three subjects used it for an increased chance of survival.

**Medical Information (Table 3)**

Twenty-nine subjects had a primary care provider (PCP) and one subject did not have a PCP. Twenty (66.7%) subjects had a medical doctor (MD, DO or MBBS) only as their PCP, and an additional five (16.7%) subjects selected MD, Nurse Practitioner (NP) and Other as their PCP. One (3.3%) subject selected MD, Naturopath, Nurse Practitioner (NP) and Other as their PCP, while one (3.3%) subject chose NP only as their PCP. One subject (3.3 %) did not indicate the type of PCP and another subject (3.3%) wrote in Physician Assistant.

The respondents had a variety of co-morbidities with hypertension, gastroesophageal reflux disease, back pain and hyperthyroidism being most frequent (data not shown). Consequently, subjects took a median of 2.5 medications with antihypertensives, analgesics, antibiotics, anti-depressants and antilipemics being the most common categories (Table 5).

**Discussion**

Patients with cancer who experience exceptional tumor responses or survival outcomes have been observed for decades but only recently have researchers attempted a comprehensive analysis of the phenomenon. NCI’s ERI solicited cases of patients meeting a set of criteria intended to identify patients with the fortuitous combination of a therapy that specifically attacked a uniquely vulnerable tumor target [1]. 111 cases were selected based on a panel’s review of approximately 4 times as many cases[2]. For 26 of these cases, there was a probable correlation between tumor genetics, the specific therapy given and the ER.

Each of the patients offered participation in this survey was identified by a clinician who felt the patient had an unexpectedly good response/survival prompting submission of a case summary to the ERI. Twelve survey subjects were excluded from enrollment in ERI for any of several different reasons including failure to strictly meet the response/survival criteria, and lack of availability or suitability of tumor tissue for genomic testing. Eighteen of the subjects included in this report met ERI criteria and were among the 111 patients discussed in the previous report of the molecular features of ERs in NCI’s program [12], however, none of them were among the 26 cases identified with a plausible “level 1” mechanistic explanation for their ER. Four categories of tumor features were identified and proposed as likely explanations for the patients’ exceptional responses/outcomes—DNA damage response, intracellular signaling pathway, prognostic genetics, and immunologic engagement [12].

Several characteristics of the study cohort were like those of the entire pool of 111 ERI subjects. Patients treated in a clinical trial represented 26.5% in NCI ERI, and 33.3% of survey participants. Two survey patients (6.7%) had ER after treatment with immune checkpoint inhibitors, while six (5.4%) NCI ERI patients had ER after treatment with immune checkpoint inhibitors. ER occurred with combination chemotherapy regimens for most of the survey patients (73.3%) and NCI ERI (68.4%) [1].

Various factors other than, or in addition to, genomic characteristics should be considered in the explanation of an ER. Spontaneous remission of cancer is a rare but well-documented phenomenon which should be considered as a potential explanation for an apparent ER [23]. An immune mechanism has been hypothesized for these remissions, but this remains unconfirmed [24].

Responses may also be due to therapies other than those under consideration as the inciting factor. Remissions after withdrawal of a hormonal therapy occur in about 30% of patients with androgen dependent prostate cancer. Such responses are generally of short duration and not profound [25,26], however, exceptions have been reported [27]. Abscopal effects from radiation therapy could also give the appearance of an ER from a systemic therapy [28]. One subject in our study had radiation therapy as part of their therapeutic regimen during the period of ER.

Several lines of research have indicated the potential of drugs not FDA-approved for cancer therapy to have anti-cancer effects in the laboratory [29], in individual patients [30] or in patient populations [31]. The use of drugs approved for non-cancer indications has occasionally been reported to be associated with unexpected, clinically significant, anticaner effects leading to laboratory investigations that discovered a potential explanatory mechanism of action [32]. Some of the drugs used by our survey subjects (e.g., beta blockers [3 subjects], metformin [1 subject]) are currently under investigation in clinical trials designed to assess if they can demonstrate significant anticaner activity. Other drugs (e.g. naltrexone), that have not yet made it into cancer
similar to percentages from other surveys of patients with cancer [36, 38]. Such maneuvers. Clinical trials are ongoing to further explore the therapeutic potential of probiotics. A variety of such products are available, and no comprehensive assessment exists of their effects in patients with cancer. Observational studies and clinical trials are beginning to explore this holistic approach to cancer care, with 60% of subjects using at least one CAM intervention resulting from tabulating the responses to the questions in the CAM section of the questionnaire, as is common in CAM surveys [9, 10, 44]. Only 8 subjects (26.7%) assessed that they used CAM and all of them answered they disclosed the use of all of their CAM interventions to at least one of their CHCPs. Our calculation of 60% of subjects using at least one CAM intervention resulted from tabulating the responses to the questions in the CAM section of the questionnaire, excluding the use of vitamins/minerals and spiritual practices. The discrepancy between this assessment and the subjects’ own assessment of what constituted CAM use negatively impacted our ability to assess the true (i.e. per protocol definition) percentage of CAM use that was disclosed to the subjects’ HCPs.

At least two of the CAM interventions used by subjects participating in this survey are of types known, under certain conditions, to have direct anticancer effects in preclinical models and/or potential therapeutic clinical effects. Huan Qin Tang, used by subject 0226, is a formulation of 4 botanicals used in traditional Chinese medicine (TCM) for at least 1800 years [45]. Researchers at Yale University began studying this herbal therapy while searching through the TCM pharmacopeia for interventions that might be useful in relieving the gastrointestinal toxicities of various chemotherapy drugs. They developed a standardized version of Huan Qin Tang, named PHY906/YIV-906, and in animal studies established its capacity to improve their quality of life, ameliorate cancer-related symptoms or treatment-related side effects or to increase their survival chances and do so throughout their post-diagnosis lives. The 60% of subjects that used CAM during the ER period seen in this study is consistent with the findings in other studies of patients with advanced cancer [43].

We found that the subjects of our study often did not consider the use of dietary supplements to be CAM (data not shown), though it was included in the CAM section of the questionnaire as is common in CAM surveys [9, 10, 44]. Only 8 subjects (26.7%) assessed that they used CAM and all of them answered they disclosed the use of all of their CAM interventions to at least one of their CHCPs. Our calculation of 60% of subjects using at least one CAM intervention resulted from tabulating the responses to the questions in the CAM section of the questionnaire, excluding the use of vitamins/minerals and spiritual practices. The discrepancy between this assessment and the subjects’ own assessment of what constituted CAM use negatively impacted our ability to assess the true (i.e. per protocol definition) percentage of CAM use that was disclosed to the subjects’ HCPs.

Recently, attention has been brought to a potential impact of a patient’s microbiome on responsiveness to cancer immunotherapy [40]. Both diet and physical activity can affect the colonic microbiota, though how to modulate these factors to provide the greatest benefit to a specific patient is unknown. Several of the subjects described here used probiotics. A variety of such products are available, and no comprehensive assessment exists of their effects in patients with cancer. Observational studies and clinical trials are beginning to explore this question, so far yielding both positive [41] and negative [42] results.

CAM is a broad range of interventions, products, personal endeavors, and health practices that have very few unifying factors other than their relative distance from the center of mainstream medical practice compared to other “conventional” therapies and practices. Patients with cancer frequently engage with CAM approaches intending to improve their quality of life, ameliorate cancer-related symptoms or treatment-related side effects or to increase their survival chances and do so throughout their post-diagnosis lives. The 60% of subjects that used CAM during the ER period seen in this study is consistent with the findings in other studies of patients with advanced cancer [43].

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decrease gastrointestinal side effects of irinotecan and other agents while, surprisingly, augmenting the tumoricidal effects of those same drugs [46]. The mucosal protective effect of PHY906 was found to be due to accelerated regeneration of intestinal progenitor or stem cells [46]. PHY906 has since been examined in early phase clinical trials in combination with various chemotherapy drugs [47].

Vitamin C (ascorbate), used by subject 0165, was first proposed as a cancer therapy in the 1970s [48], eventually leading to two NCI-supported human trials of oral ascorbate (10 g/d) which failed to demonstrate a significant therapeutic effect [49]. Subsequent research demonstrated a substantial difference in the pharmacokinetics of oral versus intravenous administration of ascorbate with peak obtainable plasma concentrations being approximately 200 nM and greater than 20 mM respectively [50,51]. Lower dose, oral ascorbate intake has been found to effect epigenetic changes in malignant cells of patients that could potentially improve responsiveness to certain cancer therapies [52]. Selective cytotoxicity of malignant cells has been seen with mM concentrations of ascorbate, both in vitro and in vivo [53,54]. Clinical trials of intravenous ascorbate alone and in combination with standard cancer therapies have been undertaken [55]. Despite the lack of definitive answers from these trials, many clinicians are administering high doses of intravenous ascorbate to patients with cancer [56].

Six subjects in our survey were treated by non-allopathic HCPs (4 homeopathic, 2 naturopathic) during the period of their ER. The details of these treatments are not available. There is very limited information from controlled clinical trials about the impact of the therapeutic approaches used by these types of HCPs on cancer response or survival [57, 58].

Despite intensive curation, the mechanistic basis for the exceptional therapeutic response could only be proposed for roughly one quarter of the patients in the ERI, suggesting that other aspects of host physiology may have contributed, some of which could have been modulated by the CAM products. Whether these or other CAM interventions played a role in the ER of any of the subjects who responded to our survey is unknown, but evidence from studies such as those mentioned here support an argument for incorporating information about the use of such interventions into the evaluation of ER cases. Some ongoing ER studies are presented here should be standard. We will not know the true explanatory potential of such information until more is gathered and approaches developed to integrate it into both the analysis of clinical trial results and ER assessments.

Conclusion

ER patients are heterogeneous and depending on how ER is defined, various scenarios could result in this designation from prolonged survival in patients receiving standard therapies (i.e., exceptional outcomes), to dramatic, unexpected therapeutic responses of bulky tumors. Multiple factors, including features of the tumor itself, the patient, or the environment, could affect survival without directly affecting the tumor’s response to therapy. Some lifestyle changes have been associated with prolonged cancer survival in certain groups of patients. Occasionally, drugs used for non-cancer indications are found to be associated with laboratory detected, or even clinically meaningful, anticancer effects. Many patients use a wide variety of CAM interventions and often attribute these “therapies” to improvement in their quality of life and duration of survival. In this burgeoning era of ER analyses, gathering medical history, lifestyle and CAM use data from patients such as those presented here should be standard. We will not know the true explanatory potential of such information until more is gathered and approaches developed to integrate it into both the analysis of clinical trial results and ER assessments.

CRediT authorship contribution statement

Oluwadamilola Olaku: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Data curation. Barbara A. Conley: Conceptualization, Resources, Project administration, Writing – review & editing. S. Percy Ivy: Resources, Project administration, Writing – review & editing. Lisa M. McShane: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. Louis M. Staudt: Conceptualization, Writing – review & editing. Sophie M. King: Data curation, Writing – review & editing. Megan Sansevere: Data curation, Writing – review & editing. Benjamin Kim: Project administration, Writing – review & editing. Jeffrey D. White: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Data curation, Funding acquisition.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.
All authors are, or were at the time the research was performed, employees of the U.S. National Cancer Institute. There was no other funding source for the study.

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