

# A literature review to investigate the link between psychosocial characteristics and treatment adherence in cancer patients

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## Abstract

Adherence to medication has been recognized as a key issue in health outcomes and efforts to improve patients' adherence are being made by the pharmaceutical industry, experts, and government bodies alike. This paper presents a review of these issues according to previous descriptive findings. Relevant studies written in English, published in 1976 or later, were identified through Medline, Embase and PsycInfo databases and reviewed. Review articles and clinical trials were excluded; all observational studies and surveys were considered. Articles were reviewed for any discussion of patients' characteristics and psychosocial characteristics affecting *adherence* to *cancer* treatment. The search strategy included a combination of key words adherence and cancer in titles. The major findings are summarized and presented under two main headings: i) patients' characteristics; and ii) psychosocial characteristics. In general, factors associated with increased likelihood of adherence to cancer treatment included younger age, higher education, higher income and Caucasian ethnicity. With regards to the psychosocial factors, lower levels of depression and anxiety, optimism as well as social support seemed to have a positive effect on treatment adherence. Studies of patterns of care in cancer treatment can help identify challenges in health care provided to particular subgroups of cancer patients and can aid researchers in designing studies that account for such factors in clinical and outcomes' research.

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## Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.<sup>1,2</sup> The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices, including smoking, physical inactivity, and *westernized* diets. With the increasing development and marketing of therapies for cancer, including the recent explosion in small molecule inhibitors that have either already been approved by the US Food and Drug Administration or are being examined in ongoing clinical trials, the issue of patient adherence has gained importance for the oncology community.<sup>3</sup>

According to the World Health Organization (WHO), *adherence is a person's behavior concerning taking medication, following a diet, and making changes in lifestyle in accordance with a medical or non-medical health professional recommendations.*<sup>4</sup> Thanks to the large body of research published over recent decades, several factors have been identified with regard to their influence on adherence behavior.<sup>5,6</sup> So far, it has been difficult to decide which factors are of the most significance and how these interact in influencing adherence behavior.<sup>7</sup> The WHO has structured recognized influential factors into five dimensions: social/economic, therapy-related, patient-related, condition-related and those related to the health-care team and system.<sup>4</sup> Key reasons for non-adherence include adverse effects or other problems with medications, such as poor instructions, poor memory, inability to pay for medications, disagreement about the need for treatment, and poor relationships between consumers and healthcare professionals.<sup>8-10</sup> Other reasons for non-adherence include polypharmacy,<sup>11</sup> low literacy,<sup>12</sup> *silent* conditions such as hyperlipidemia, hypertension and osteoporosis,<sup>13</sup> cultural factors,<sup>14</sup> inadequate social support,<sup>15</sup> depression,<sup>16,17</sup> health beliefs<sup>18,19</sup> or patients' personality.<sup>20</sup>

A review of the research into cancer therapy and patient adherence showed that it has mainly focused on non-adherence to taking chemotherapy medication and attending medical appointments, whereas there is very little research on adherence for other behavioral aspects of therapy (*e.g.* fluid intake, weight maintenance, etc.) that are relevant across all cancers. Some studies have examined adherence to certain behavioral aspects for a specific cancer (*e.g.* adherence to toothpaste or gel fluoride treatment for head and neck cancers).<sup>21</sup> However, the prevalence and assessment of non-adherence to a wide range of behavioral aspects common across all cancers has not been extensively examined. Because of their importance in promoting patient health and quality of life (QoL), these aspects deserve further attention.

Numerous studies have examined the factors affecting how cancer patients receive treatment but for the moment there is no literature available that compiles factors associated with patients' characteris-

tics and psychosocial characteristics in a single source. For example, it is commonly understood that older patients are generally less likely to receive cancer treatment due to their shorter life expectancies, general poorer health and the reduced risk/benefit. However, other factors may also influence receipt of treatment, even in younger patients, and need to be accounted for in observational studies and research into outcomes involving cancer. Therefore, we performed a review of the literature and information published since 1976 regarding the factors affecting treatment adherence in patients with cancer, taking into account patients' characteristics and psychosocial characteristics.

## Materials and Methods

Published data assessing adherence in cancer patients from the past 35 years (from 1976 to 2010) was searched for in Medline, Embase and PsycInfo databases including the following terms: *adherence*, *cancer*, *psychosocial characteristics* and *patient characteristics*. Review articles, case reports and clinical trials were excluded; observational, clinical, and population-based studies were considered, as were survey data of physicians and oncologists. General clinical reviews that provided treatment guidelines but no original data were also excluded. The factors studied in relation to receipt of cancer treatment were roughly divided into two primary categories: patients' characteristics and psychosocial characteristics.

In order to have a more integrated view on the topic of adherence, we have also reported some results concerning the adherence in a more general context, that is the field of chronic diseases other than cancer.

## Results and Discussion

Several variables have been found to be associated with adherence to cancer treatment. Some commonly cited variables are education,<sup>22</sup> income,<sup>22</sup> emotional states<sup>23-25</sup> and complexity of the treatment regime.<sup>26</sup> In addition, optimism has been found to be associated with adherence to medication taking,<sup>27</sup> but has not been examined with adherence to cancer treatment regimens. The relevant studies that have examined the patient and psychosocial variables in relation to adherence are summarized below.

### Patients' characteristics

#### Age

Most of the studies showed that age was related to adherence in chronic diseases, although a few researchers found age not to be a factor causing non-adherence.<sup>28-31</sup> For elderly people, the results from the various studies are not unidirectional. A large proportion of retrieved studies suggested that they might have higher adherence.<sup>32-45</sup> However, in contrast, some studies found that advancing age affected adherence among elderly people in a negative way.<sup>46-48</sup> Regarding cancer treatment, all of the studies examined found that older patients received chemotherapy showed less adherence than younger patients.<sup>49-57</sup> Of these studies, 7 provided numerical data to support this conclusion.<sup>50-54,56,57</sup> Five of the studies demonstrated a statistically significant difference in chemotherapy use between older and younger patients,<sup>51-54,56</sup> although only 2 of these provided data specific to metastatic cancer.<sup>52,53</sup> In a prospective survey of qualified specialists in France, the authors noted that, of the women receiving chemotherapy, 82% in the younger age group received the standard dose and cycle length compared with only 62% of those in the older age group.<sup>53</sup> In a survey administered to medical and clinical oncologists in the UK, ask-

ing which factors were important in deciding whether to recommend chemotherapy to patients with metastatic breast cancer, patient age was considered to be *quite important* or *very important* for 58.6% of oncologists surveyed.<sup>58</sup>

Several studies offered reasons to explain why older women were less adherent to chemotherapy. The lower proportion of older women with breast cancer receiving chemotherapy may reflect an increased number of co-morbidities and worse general health among these women.<sup>53</sup> For example, among British oncologists, *frailty* and *concurrent medical conditions* were considered *quite important* or *very important* to 93.1% and 82.8% of surveyed clinicians, respectively, compared to the 58.6% of oncologists who considered age to be of importance.<sup>58</sup> Of the 10 studies in this review citing the impact of age on chemotherapy use, only two adjusted for co-morbidities,<sup>51,52</sup> one of which<sup>18</sup> provided data specific to metastatic breast cancer. In both studies, multivariate analyses revealed a stronger inverse association of increasing age and chemotherapy use than that of co-morbidity and chemotherapy use. The higher prevalence of hormone receptor (estrogen or progesterone receptor) positive tumors among postmenopausal women than premenopausal women<sup>59</sup> and, therefore, more frequent use of hormone therapy, also contributes to this observation. It has been suggested that elderly patients have cancers with lower proliferative indices, and that they will derive less benefit from standard chemotherapy;<sup>60</sup> however, the elderly are frequently underrepresented in cancer clinical trials. Although elderly (65 years of age or older) patients make up 63% of cancer patients in the US, they represent only 25% of the cancer clinical trial participants.<sup>61</sup> Whether this deficit is due to fear and misunderstanding of older patients, physician bias against enrolling older patients, or overly stringent eligibility criteria that limit the number of elderly patients, their underrepresentation makes it difficult to assess the risks and benefits of cancer chemotherapeutic regimens and may partially explain the inverse relationship between age and chemotherapy use. Also, elderly patients may have problems in vision, hearing and memory. In addition, they may have greater difficulty in following therapy instructions due to cognitive impairment or other physical difficulties, such as having problems in swallowing tablets, opening drug containers, handling small tablets, distinguishing colors or identifying markings on drugs.<sup>62-69</sup>

#### Education

Several studies found that better educated patients might have higher adherence,<sup>70-72</sup> while some studies found no association.<sup>73-78</sup> Intuitively, it may be expected that patients with higher levels of education should be better informed about the disease and therapy and, therefore, demonstrate greater adherence. However, Di Matteo found that even highly educated patients may not understand their medical condition or may not perceive the benefits of adherence to their medication regimen.<sup>79</sup> Other researchers showed that patients with lower levels of education show better adherence.<sup>80</sup> Four studies discussed education level in relation to chemotherapy treatment,<sup>81,58,55,56</sup> as well as other adjuvant therapies, such as radiation and hormone therapy; only 2 provided quantitative data related to chemotherapy,<sup>82,55,56</sup> and only one was specific to metastatic breast cancer.<sup>58</sup> Peele and colleagues stated that educated women were significantly more likely to adhere to treatment with adjuvant therapy, including chemotherapy, hormone therapy, and combination therapy, although the study did not distinguish between cases based on disease severity and treatment.<sup>56</sup> Mitchell and colleagues reported that being less educated was statistically significantly and inversely correlated to a belief in *religious intervention in place of treatment*;<sup>55</sup> it is presumed that the treatment likely included chemotherapy due to inclusion of women with advanced-stage breast cancer in the study population. From a qualitative perspective, Ashing-Giwa and colleagues, when discussing various adjuvant

therapies including chemotherapy, reported that less-educated women in the United States were less informed about breast cancer itself, as well as about resources and treatments. They were less adherent to treatment and less proactive in seeking medical care.<sup>81</sup> In the UK, 13.8% of clinicians ranked education as an important factor influencing their recommendation for palliative chemotherapy to women with metastatic breast cancer.<sup>58</sup>

#### Cost of therapy and income

Cost is a crucial issue in patient adherence especially for patients with chronic disease as treatment could be life-long.<sup>83-86</sup> Healthcare expenditure could be a large portion of living expenses for patients suffering from chronic disease. Cost and income are two interrelated factors. Healthcare cost should not be a heavy burden if the patient has a relatively high income or health insurance. A number of studies found that patients who had no insurance cover,<sup>87-89</sup> or who had low income,<sup>90-95</sup> were more likely to be non-adherent to treatment. However, even for patients with health insurance, health expenses could still be a problem. More than one in 10 senior citizens in the USA reported using less of their required medications because of cost.<sup>96</sup> Nevertheless, in other cases, income was not related to adherence level.<sup>97-100</sup> Three studies discussed income in relation to chemotherapy treatment: 2 in the US<sup>101</sup> and one in the UK.<sup>102</sup> Of the 2 studies that provided numerical data, neither observed a significant difference in the proportions of patients receiving chemotherapy by income, although one suggested that their observation that uninsured, lower income women were less likely to adhere to chemotherapy may have reached statistical significance with a larger sample size. A qualitative study of community health professionals working with different patient populations reported that individuals with lower income may not have sufficient awareness of the disease, resources, and treatments, and are not as proactive about seeking medical care.

#### Ethnicity

Race as a factor causing non-adherence has been studied fairly widely in the USA and European countries. Caucasians are believed to have good adherence according to some studies,<sup>103-106</sup> while African-Americans, Hispanics and other minorities were found to have comparatively poor adherence.<sup>107-113</sup> However, a plausible explanation for this may be due to the patients' lower socio-economic status and language barriers affecting the minority ethnic races in the study countries. Hence, due to these confounding variables, ethnicity may not be a true predictive factor of poorer adherence. Five studies, all conducted in the US, considered race to be a factor in predicting adherence to chemotherapy in breast cancer patients.<sup>52,55,81,114,115</sup> Only one study presented data specific to metastatic breast cancer,<sup>52</sup> with the remainder considering all cases (stages I through IV) in aggregate. In a study by Du and Goodwin,<sup>52</sup> the proportions of black and white women with stage IV breast cancer who received chemotherapy were similar (26.8% *vs.* 26.5%, respectively), although fewer women whose race was classified as *other* received chemotherapy (18.2%). Two other studies (not specific to stage IV disease) reported very small differences in the percentages of Caucasian, African-American, and Hispanic women with breast cancer treated with chemotherapy; both noted that higher proportions of Caucasian women (81.3% and 67.0%) than African-American women (80.0% and 46.5%) or Hispanic women (52.4%) received chemotherapy,<sup>114,115</sup> although these differences either were not statistically significant or statistical significance was not evaluated.<sup>115</sup>

#### Psychosocial characteristics

##### Emotional states: depression, anxiety and adherence

Research has indicated that emotional states such as depression

and anxiety may be associated with adherence. A recent meta-analysis conducted across medical regimens by Di Matteo, Lepper, and Crogham<sup>116</sup> reported that depressed patients were 3 times as likely as non-depressed patients to be non-adherent, but found that anxiety was not significantly associated with adherence. A few studies on cancer therapy regimens have examined the relationship between emotional states and adherence. For example, Ayres *et al.*<sup>117</sup> prospectively examined psychosocial aspects in order to predict adherence to administered chemotherapy appointments for grade IV cancer. Using discriminant analysis, patients who exhibited more anxiety and depression were more likely to adhere by attending chemotherapy appointments. Furthermore, Richardson *et al.*<sup>24</sup> found that depression at six months was significantly correlated with non-adherence in patients who took oral chemotherapy medication intermittently. Finally, Itano *et al.*<sup>23</sup> found that those with higher state anxiety were more likely to adhere to attending chemotherapy and blood laboratory work appointments.

In summary, most research indicates that depression plays an important part in predicting non-adherence. From a conceptual standpoint, it can be postulated that depression may affect cognitions (*e.g.* outcome expectancies, perceived benefits and barriers) and motivation to follow through with treatment recommendations. However, the role that anxiety plays with regard to adherence is less clear. Across medical regimens, research has indicated that anxiety has had no significant effect on adherence. However, some of the research into cancer and adherence has indicated that anxiety is positively correlated with adherence. Some have argued that anxiety can be associated with enhanced adherence because anxious individuals have been shown to be more hypervigilant and have an increased tendency to seek medical assistance.<sup>118</sup>

##### Optimism and adherence

Optimism has been found to predict a better QoL<sup>119</sup> and promote lower distress levels among breast cancer patients.<sup>120</sup> With regard to adherence, some research has indicated that optimism is associated with a more positive attitude toward medication taking.<sup>121</sup> Carver, Lehman and Antoni<sup>122</sup> argued that optimism keeps patients involved and engaged in treatment goals, leading to an improved psychological well-being. It also seems likely that optimistic patients focus on positive aspects of treatment, or benefits, and are more likely to adhere.

##### Social support/partners

The general findings from these articles showed that patients who had emotional support and help from family members, friends or healthcare providers were more likely to be adherent to the treatment.<sup>123-133</sup> The social support helps patients in reducing negative attitudes to treatment, being motivated and also remembering to implement the treatment. Two studies provided numerical data regarding the impact of a spouse or significant other on the adherence to chemotherapy treatment<sup>52,82</sup> one of which provided data specific to metastatic breast cancer.<sup>52,18</sup> Osborne *et al.* reported that married women were more likely to adhere to chemotherapy than unmarried women (married 12.3% *vs.* unmarried 9.1%). Du and Goodwin also reported similar findings (married 37.4% *vs.* unmarried 20.7%). One study suggested that unmarried women might receive chemotherapy less often due to patients' personal concerns over postoperative assistance and transportation or the amount of out-of-pocket expense for treatment, or due to a doctor's decision not to discuss such treatment options because of these assumptions.<sup>82</sup> Of British clinicians surveyed, 51.7% reported that the patient's social support was an important factor in their decision to give palliative chemotherapy to women with metastatic breast cancer.<sup>58</sup>

Details of studies included in the review are listed in Table 1.

## Conclusions

In this review, we attempted to identify general factors related to adherence. Original studies investigating adherence in cancer patients were retrieved. However, in order to have a more integrated view on the specific topic, we have also reported some results from different diseases, population settings and different countries. In the process, we identified a wide array of influencing factors. Although the effect of some factor on adherence is complex and not unequivocal, the review process has identified several factors with consistent impact on adherence. Factors affecting receiving treatment in patients with cancer have been well studied, but for the moment there is no literature available that compiles factors associated with patients' characteristics and

psychosocial characteristics in a single source.

The effect of demographic factors (*e.g.* age, ethnicity and educational level) on adherence is complicated by the fact that they may not be truly independent. In fact, demographic factors are related to patient cultural, socioeconomic and psychological backgrounds. Thus, future studies on adherence should not focus on demographic factors alone. Psychosocial factors such as psychological well-being, social support, patients' beliefs and their motivation regarding therapy could be classified as *crucial* factors. Since the 1990s, research has focused more on the patient-provider relationship, patient's mental health and patient's beliefs about their therapy. For individuals with chronic diseases, and specifically in cancer patients, a favorable quality of life would enhance their treatment adherence. In fact, the effects of patient's beliefs, emotional states, health knowledge and relationship with the healthcare

**Table 1. Details of the studies included in the review.**

Study	Type of study	Patients	Age (years)	Statistical analysis	Factors of adherence
Caban <i>et al.</i> <sup>49</sup>	Population-based	234	56 (range 24-86)	Hierarchical Logistic Regression	Age
Diab <i>et al.</i> <sup>50</sup>	Study population	307.115	≥55	Linear Associations	Age
Du <i>et al.</i> <sup>51</sup>	Population-based	35.060	≥65	Multivariate analysis	Age
Du <i>et al.</i> <sup>52</sup>	Study population	1.129	≥65	Logistic regression	Age, ethnicity, social support
Freyer <i>et al.</i> <sup>53</sup>	Prospective survey	1.009	500 from 65 to 74 (average 68.6) and 509 >75 (average 79.6)	Correlation	Age
Golledge <i>et al.</i> <sup>54</sup>	Study population	784	≥60	Correlation	Age
Mitchell <i>et al.</i> <sup>55</sup>	Clinical	682	≥40	Factor analysis	Age, education, ethnicity
Peele <i>et al.</i> <sup>56</sup>	Clinical	386	Not stated	Not stated	Age, education
Wyld <i>et al.</i> <sup>57</sup>	Clinical	378	55-69 and >70 (comparative study)	Statistical significance tested with $\chi^2$	Age
Dunnwald <i>et al.</i> <sup>59</sup>	Population-based	155.175	≥30	Multivariate Cox regression modelling	Age
Hutchins <i>et al.</i> <sup>61</sup>	Population-based	16.396	>65	Two-tailed P values	Age
Benner <i>et al.</i> <sup>62</sup>	Retrospective cohort	35.401	>65	Generalized linear models for repeated measures	Age
Chizzola <i>et al.</i> <sup>63</sup>	Clinical	485	54 (range 17-86)	Chi-square test, students t-test, multivariate log-line or regression analysis	Age
Theofilou <sup>64</sup>	Clinical	168	62	Independent-samples t-test, one-way ANOVA, correlation	Age
Jeste <i>et al.</i> <sup>65</sup>	Clinical	110	Not stated	Stepwise regression analysis	Age
Murray <i>et al.</i> <sup>66</sup>	Clinical	140	Not stated	Not stated	Age
Nikolaus <i>et al.</i> <sup>67</sup>	Clinical	119	Not stated	Not stated	Age
Okuno <i>et al.</i> <sup>68</sup>	Clinical	220	≥60 (mean age of 75.7)	Multiple logistic regression analysis	Age
Ashing-Giwa <i>et al.</i> <sup>81</sup>	Clinical	102	Not stated	Not stated	Education, ethnicity
Osborne <i>et al.</i> <sup>82</sup>	Population-based	32.268	≥65	Not stated	Education, social support
Liu <i>et al.</i> <sup>101</sup>	Population-based	13.703	Not stated	Logistic regression	Income
Downing <i>et al.</i> <sup>102</sup>	Population-based	12.768	Not stated	Logistic regression and Cox proportional hazards analyses	Income
Maloney <i>et al.</i> <sup>114</sup>	Clinical	52	56.6	Chi-squared and tailed t-tests	Ethnicity
Shavers <i>et al.</i> <sup>115</sup>	Epidemiology	3.978	21-34	Multivariate analyses	Ethnicity
Richardson <i>et al.</i> <sup>24</sup>	Clinical	92	18-86	Not stated	Emotional states
Carver <i>et al.</i> <sup>119</sup>	Clinical	163	Not stated	Correlation and multivariate analyses	Optimism
Epping-Jordan <i>et al.</i> <sup>120</sup>	Clinical	80	Not stated	Regression analyses	Optimism
Godin <i>et al.</i> <sup>121</sup>	Clinical	376	Not stated	Regression analyses	Optimism
Carver <i>et al.</i> <sup>122</sup>	Clinical	235	27 to 87 (mean age of 53.59)	Regression coefficients	Optimism

ANOVA, analysis of variance.

provider are very complex because these factors are interrelated with each other. The interaction is a little like antibiotic combinations. Sometimes the effect is additive or synergistic while other times the effect is antagonistic. However, due to the design of the studies performed so far, it is difficult, if not impossible, to differentiate precisely between whether the interaction between these factors has been additive, synergistic or antagonistic. More robust and better designed studies would be needed in future to clarify these interactions. Certainly, there are some limitations in the current review. Three electronic databases, Medline, Embase and PsycInfo, were searched and only English articles were included. It might be possible that some informative studies in other literature databases or in other languages were omitted. Also, from the review of the literature starting from the 1970s to identify relevant factors relating to therapeutic adherence, the evidence indicates that non-adherence is still commonplace and no substantial change has occurred despite the large number of studies attempting to address and highlight the problem. In addition, too few studies are being carried out systematically to quantify the impact of non-adherence on health and financial outcomes. The magnitude of the impact of non-adherence needs to be studied in future research due to the potentially enormous implications of poor adherence on clinical and economic outcomes. Finally, few studies on adherence have been performed in Asia and developing countries where most of the world's population now lives. More studies on factors influencing adherence in these countries or regions would be helpful to fill the gap in our knowledge and help formulate international strategies to reduce non-adherence.

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