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# A Coala-T-Cannabis Survey Study of Breast Cancer Patients' Use of Cannabis Before, During, and After Treatment

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**BACKGROUND:** The goal of this study was to characterize cannabis use among patients with breast cancer, including their reasons for and timing of use, their sources of cannabis information and products, their satisfaction with the information found, their perceptions of its safety, and their dialogue about cannabis with their physicians. **METHODS:** United States-based members of the Breastcancer.org and Healthline.com communities with a self-reported diagnosis of breast cancer within 5 years (age  $\geq$  18 years) were invited to participate in an anonymous online survey. After informed consent was obtained, nonidentifiable data were collected and analyzed. **RESULTS:** Of all participants (n = 612), 42% (n = 257) reported using cannabis for relief of symptoms, which included pain (78%), insomnia (70%), anxiety (57%), stress (51%), and nausea/vomiting (46%). Furthermore, 49% of cannabis users believed that medical cannabis could be used to treat cancer itself. Of those taking cannabis, 79% had used it during treatment, which included systemic therapies, radiation, and surgery. At the same time, few (39%) had discussed it with any of their physicians. **CONCLUSIONS:** A significant percentage of survey participants (42%) used cannabis during active cancer treatment despite the potential for an adverse event during this vulnerable time. Furthermore, most participants believed that cannabis was safe and were unaware that product quality varied widely and depended on the source. This study reviews the research on medicinal cannabis in the setting of these findings to help physicians to recognize its risks and benefits for patients with cancer. **Cancer 2022;128:160-168**. © *2021 American Cancer Society*.

#### LAY SUMMARY:

• Almost half of patients with breast cancer use cannabis, most commonly during active treatment to manage common symptoms and side effects: pain, anxiety, insomnia, and nausea.

• However, most patients do not discuss cannabis use with their physicians. Instead, the internet and family/friends are the most common sources of cannabis information.

• Furthermore, most participants believe that cannabis products are safe and are unaware that the safety of many products is untested.

KEYWORDS: breast cancer, cannabis, marijuana, palliation.

#### INTRODUCTION

Breast cancer treatment advances have significantly reduced mortality.<sup>1</sup> However, patients still experience symptoms and side effects that impair their quality of life; this can reduce treatment adherence and worsen the prognosis.<sup>2</sup> Many patients with cancer turn to cannabis for symptomatic relief<sup>3-5</sup> because of its reported ability to lessen pain, nausea, and anorexia from cancer or its treatments.<sup>6</sup> Cancer is specified as a qualifying condition in nearly all states with medical cannabis programs.<sup>7</sup> However, shared decision-making between clinicians and patients on cannabis use is lacking.<sup>8</sup>

We investigated patterns of cannabis use among participants with a self-reported diagnosis of breast cancer who were members of our online health communities (Breastcancer.org and Healthline.com). We used an anonymous online survey to elicit frank responses. Participants were asked about their reasons for cannabis use and whether they used it during active treatment for their cancer. We also asked about their sources of cannabis to understand whether medically ill patients were using regulated cannabis that had been tested for purity and contaminants. Lastly, we asked participants about their perceptions on the safety of cannabis and their sources of information because a previous study showed that 75%

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of patients rely on the internet for medical recommendations on cannabis.<sup>9</sup> However, much of this information is unregulated and not evidence-based.

Many physicians feel that they lack the knowledge needed to discuss cannabis with their patients. A national survey of 400 medical oncologists reported that 70% felt unprepared to discuss cannabis use and to make clinical recommendations for their patients.<sup>10</sup> To bridge this gap, we review our survey findings in the setting of the current research on the risks and benefits of cannabis to help practitioners to discuss this with their patients.

# MATERIALS AND METHODS

A 47-question survey was developed via a literature review and discussions with oncologists, cannabis researchers, statisticians, and patients (see the supporting information). Demographic variables included age, sex, geographic region, and breast cancer variables (time since diagnosis, hormone receptor and HER2 status, stage, and current treatment status). Patterns of cannabis use were assessed through questions about reasons for use, timing of use (before, during, and/or after treatments), types of products used, and sources of cannabis. Participants were also asked about their information sources and willingness to discuss cannabis with providers.

Between December 16, 2019, and January 19, 2020, United States-based members of the community of Breastcancer.org (a nonprofit, internet-based organization that provides medical information and peer support) were invited to participate in the survey through Breastcancer.org's community message boards, homepage, social media, and email newsletter. Healthline.com, a Breastcancer.org partner and a leading source of online health information, invited its community to participate during the last week of recruitment to boost accrual to more than 500 patients within the time frame of this study.

All survey responses were self-reported; this included the eligibility requirements, which were an age  $\geq$  18 years, US residency, and a breast cancer diagnosis within 5 years. Otherwise, participants were unselected. After informed consent was obtained, nonidentifiable, participant-reported data were collected without electronic medical record verification. The data were then analyzed in aggregate.

Survey responses and data comparisons were summarized as frequencies and percentages for categorical variables and as medians and ranges or as means and SDs for continuous variables. Continuous and categorical distributions were compared between 2 independent groups with the 2-sample *t* test and  $\chi^2$  test of independence, respectively. Several survey questions were formatted on a Likert scale of 1 to 5, and responses were analyzed on the individual Likert scale and also after the top 2 categories (Likert scores of 4 and 5) and the bottom 2 categories (Likert scores of 1 and 2) had been collapsed. Analyses were performed with SPSS-MR Quantum. A significance level of .05 (2-sided) was used for all analyses. We received IRB approval prior to initiation of the survey study.

### RESULTS

Overall, 4354 people viewed the survey invitation, 3522 initiated screening, 832 completed screening, 725 met the eligibility criteria, and 612 consented and completed the survey (response rate, 84% [612 of 725]). The mean completion time was 14 minutes. Of the survey completers (n = 612), 82% were recruited from Breastcancer.org, and 18% were recruited from Healthline.com. The mean age was 57 years (range, 27-84 years) with 605 females, 5 males, and 2 who preferred not to answer per self-reporting. All states were represented except for Montana, North Dakota, South Dakota, and Mississippi, and the participants reflected the population density of the United States.

The total number of survey completers was 612, and 257 (42%) reported having used cannabis to address medical issues. As shown in Table 1, only 23% of the 257 participants (n = 58) reported using cannabis only for medical purposes (relief of symptoms stemming from their illness or its treatments), whereas 77% (n = 199) reporting using cannabis for medical or recreational reasons (to socialize, to feel intoxicated, for fun or relaxation, or out of curiosity). Table 1 also shows the age, sex, months since diagnosis, and current status of breast cancer treatment for the participants.

#### Information on Cannabis

All participants (n = 612) were asked about their level of interest in cannabis use for medical purposes. Of these, 64% reported that they were very or extremely interested in the topic, 23% were somewhat interested, and 13% were minimally or not interested. Half of all participants (306 of 612) had sought information on medical cannabis and were asked to rank the single most helpful source of information that they found. As shown in Table 2, these sources ranged from websites to other patients with breast cancer, whereas few listed a clinician. Of those who sought information on cannabis use for medical purposes (n = 302), most were unsatisfied with the information that they received. In our survey, only 6% were extremely

TABLE 1.	Participant	Demographics
	rancipant	Demographics

	Total (n = 612)	Medical Cannabis Only $(n = 58)$	Medical or Recreationa Cannabis (n = 199)
Age, mean (SD), y	56.7 (±10.1)	56.8 (±11.2)	55.5 (±10.1)
Sex, % (No.)			
Female	99 (605)	100 (58)	98 (196)
Male	1 (5)	0 (0)	2 (3)
Prefer not to answer	<1 (2)	0 (0)	0 (0)
Months since most recent breast cancer diagnosis, mean (SD)	20.1 (±17.2)	17.7 (±14.9)	21.5 (±16.8)
Current status of breast cancer treatment, % (No.)			
In treatment before surgery	10 (63)	7 (4)	11 (21)
In treatment after surgery	46 (282)	45 (26)	40 (80)
Finished treatment	27 (164)	22 (13)	30 (59)
Ongoing treatment for advanced/metastatic breast cancer	16 (98)	26 (15)	20 (39)
Stopped treatment for advanced/metastatic breast cancer	1 (5)	- (0)	- (0)

Age and time since diagnosis are provided as means and SDs. Sex and treatment status are provided as percentages and numbers of participants. The columns include all participants, those reporting cannabis use for medical purposes only, and those reporting cannabis use for medical and recreational purposes.

satisfied and 25% were very satisfied with the information, whereas the rest were only somewhat satisfied (44%), minimally satisfied (19%), or dissatisfied (6%).

Of all participants, 39% discussed cannabis with any of their physicians, and 76% of these discussions were patient-initiated. Older participants were more likely to ask their physician about cannabis: 87% of those older than 66 years asked for guidance, whereas 76% of those aged 50 to 65 years and 69% of those younger than 50 years did (*P* for age > 66 years vs age < 50 years = .03). However, 28% of all survey participants were uncomfortable with discussing cannabis with their physician. Among those who discussed cannabis with their physicians, younger patients were more likely to feel that their physicians were supportive: 72% of those younger than 50 years felt that their physician was extremely or very supportive, whereas 52% of those aged 50 to 65 years (*P* = .03) and 46% of those aged  $\geq$ 66 years (*P* = .03) did.

## Cannabis Use and Symptoms

The participants who used cannabis (n = 257) for medical purposes reported that they used it for the following symptoms: pain (acute and chronic joint and muscle aches, discomfort, stiffness, or nerve pain; 78%), insomnia (70%), anxiety (57%), stress (51%), and nausea/vomiting (46%; see Fig. 1). Of cannabis users, 75% reported that it was extremely or very helpful at relieving their symptoms. Additionally, 57% said that they had found no other way of treating their symptoms. We also looked at the effect of the participants' age with respect to their reports of finding cannabis useful for treating symptoms (n = 257): 62% of those older than 66 years reported experiencing a benefit, whereas 72% of those between 50 and 65 years and 86% of participants younger than 50 years did. These differences were significant: More of those younger than

### **TABLE 2.** Half of Study Participants (306 of 612) Sought Information on Medicinal Cannabis and Were Asked to Select the Single Most Helpful Source of Information

	Total (n = 306)
Source of Cannabis Information	% (No.)
Websites	22 (67)
Family member or friend	18 (56)
Nonpharmacist dispensary staff member (eg, budtender)	12 (37)
Pharmacist in dispensary	12 (36)
Another patient with breast cancer	7 (21)
Nonphysician or nonnurse health care provider (eg, chiro- practor or acupuncturist)	6 (18)
Physician	4 (12)
Movies or documentaries	3 (8)
Nurse	2 (7)
Coworker or colleague	2 (7)
Advertisements	1 (4)

50 years found that cannabis was helpful in comparison with those aged 50 to 65 (P = .05) or  $\ge 66$  years (P = .04).

# Cannabis Use During Treatment

Among the 257 participants who reported cannabis use, 24% (61 of 257) reported using it before active treatment began, 79% (204 of 257) reported using it during treatment, and 54% (139 of 257) reported use after the completion of treatment. Table 3 shows the phases of treatment during which cannabis was used, which included systemic treatments, surgery, and radiation. Lastly, of the 257 participants who reported using medical cannabis, 49% (126 of 257) stated that one reason for using cannabis was to treat the cancer itself (beyond symptom management).

# Sources of Cannabis

Participants reporting cannabis use (n = 279) said that they obtained it from a range of sources, including edibles





# **TABLE 3.** Phase of Treatment During Which Cannabis Was Used Among Those Who Used Cannabis During Treatment

	Total (n = 204) % (No.)	
Treatment		
Chemotherapy (n = 148)	86 (127)	
Targeted therapy or immunotherapy for advanced/metastatic breast cancer (n = 35)	83 (29)	
Anti-HER2 therapy (n = 45)	71 (32)	
Hormonal therapy $(n = 140)$	65 (91)	
Mastectomy alone $(n = 45)$	51 (23)	
Radiation to the breast area (n = 120)	49 (59)	
Radiation to other parts of the body ( $n = 30$ )	47 (14)	
Lumpectomy (n = 87)	40 (35)	
Mastectomy and reconstruction ( $n = 63$ )	38 (24)	

<b>TABLE 4.</b> Cannabis Users' Sources of Products by the Legality of Cannabis in Their	State
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Source of Cannabis Products	Total (n = 257), % (No.)	Medical Cannabis Legal in State (n = 216), % (No.)	Medical Cannabis Not Legal in State (n = 41), % (No.)
Medical cannabis dispensary	54 (138)	60 (130)	20 (8)
Friend or family member	33 (86)	29 (62)	59 (24)
Recreational cannabis dispensary	27 (70)	27 (59)	27 (11)
Dealer	6 (15)	3 (7)	20 (8)
Delivery service	5 (13)	5 (11)	5 (2)
Home grown	5 (13)	5 (10)	7 (3)
Over-the-counter source (eg, drug store)	4 (10)	3 (6)	10 (4)
Online dispensary	4 (11)	5 (10)	2 (1)

(70%), liquids/tinctures (65%), smoking (51%), topicals (46%), and vape pens (45%). Participants also reported using an average of 3.7 different products (SD, 4.2; median, 2). Table 4 shows the sources of cannabis by the legality of medical cannabis in the state where the participants lived.

A preference for cannabidiol (CBD) versus  $\Delta$ -9tetrahydrocannabinol (THC) products was reported by participants: 22% preferred CBD only, 21% preferred mostly CBD, and 19% preferred an equal ratio of THC to CBD. Only 26% preferred THC-dominant products. No preference was reported by 7%. Nonetheless, many respondents did not understand the difference between CBD and THC derived from hemp versus marijuana products (40% of cannabis users and 65% of nonusers did not know; P = .04) or the difference between THC and CBD (18% of cannabis users and 46% of nonusers; P = .03).

Participants Who Reported "Somewhat or Strongly Agree" to the Following Questions	Total (n = 612), % (No.)	Medical Cannabis User Only (n = 58), % (No.)	Medical and Recreational Cannabis (n = 199), $\%$ (No.)
Medical cannabis should be viewed similarly to other plant-based medicines (eg, aspirin).	78 (476)	78 (45)	85 (169)
I am looking for more natural products to treat my symp- toms rather than chemicals.	76 (464)	78 (45)	83 (165)
The benefits of medical cannabis outweigh the risks.	71 (432)	74 (43)	84 (168)
I am interested in medical cannabis to reduce or eliminate my need for opioids.	47 (288)	66 (38)	54 (108)
I feel there is a stigma around using medical cannabis.	44 (270)	40 (23)	52 (103)
I am interested in medical cannabis because I have no other way of treating some symptoms related to my breast cancer situation.	41 (250)	57 (33)	51 (101)
I do not feel comfortable approaching the subject of medi- cal cannabis with my doctor.	28 (171)	14 (8)	24 (48)

### TABLE 5. Participants' Perceptions of Cannabis for Medical Purposes

# Perceived Safety of Cannabis

Participants' opinions on cannabis for medical purposes are shown in Table 5 (n = 612). The majority of the participants (>70%) believed that cannabis should be viewed as a plant-based medicine, that natural products were better than "chemicals," and that the benefits of cannabis outweighed the risks. Participants' opinions on the differences between medical and recreational cannabis sources were as follows: 73% believed that medical cannabis, whereas 25% thought that they were equally "clean/pure." Furthermore, 64% believed that medical cannabis was safer than recreational cannabis, whereas 35% believed that there was no difference.

# DISCUSSION

The results of our study show that, among breast cancer participants, there is a strong interest in medicinal cannabis, and almost half reported using it. The most common reasons included pain, insomnia, anxiety or stress, and nausea/vomiting. Among those using cannabis for these purposes, the majority reported that it provided relief and that they had no other effective way of treating their symptoms. Additionally, many participants used cannabis during cancer treatment and believed that cannabis may have anticancer benefits, although few had discussed it with their physicians. Lastly, the cannabis-using participants reported using a wide range of different products, which are known to vary in quality and purity. Most felt that cannabis products were natural and safe and were unaware of the potential risks of contaminants, drug-drug interactions, or the prevalence of mislabeled merchandise.

Here, we discuss our findings in the context of the current research on medicinal cannabis to help practitioners to improve their ability to discuss the issue with patients, including the risks and potential benefits.

# Cannabis Use and Symptom Relief

Previous studies have investigated the percentage of patients with cancer using cannabis at individual treatment centers and have reported a wide range (16%-56%).<sup>3-5</sup> Our study included a national sample, and we found that 42% of patients with breast cancer were using cannabis. Nonetheless, across all studies, pain, anxiety, and nausea are the most common reasons for using cannabis.<sup>3,5</sup> This raises the question of whether the research supports the use of cannabis for these symptoms.

Although the cannabis plant contains hundreds of cannabinoids, the most studied are THC and CBD. THC has psychoactive effects, such as intoxication, mood elevation, and sedation. In contrast, CBD produces few subjective effects, although it can be sedating in very high doses.<sup>11</sup> THC has been more widely studied than CBD, and overall, data support the use of THC for pain and nausea/vomiting. In 2017, the National Academy of Sciences, Engineering, and Medicine published a report on the health effects of cannabis; it found substantial support for the use of THC-containing products for chronic pain (including cancer and neuropathic pain) and for chemotherapy-induced nausea and vomiting.<sup>12</sup> The THC products included the cannabis plant, cannabis plant extract, and the Food and Drug Administration (FDA)-approved drugs dronabinol (manmade THC) and nabilone (THC synthetic analogue). Dronabinol and nabilone are FDA-approved for chemotherapy-induced nausea and vomiting and have efficacy comparable to standard treatments.<sup>13</sup>

Additional studies support the use of THC for insomnia and anxiety. THC alleviates sleep problems by improving sleep quality and restfulness in patients with sleep apnea, chronic noncancer pain, and multiple sclerosis.<sup>13,14</sup> THC has also been shown to reduce anxiety in medically ill patients, including those with chronic noncancer pain,

Cancer

Tourette disorder, and multiple sclerosis.<sup>13-15</sup> However, in those studies, anxiety was a secondary end point, not a primary outcome measure; this means that studies are needed that directly investigate this effect.

As for CBD, research on pain, anxiety, and sleep is scarce. Studies have shown that CBD improves chemotherapy-induced neuropathic pain in rodents<sup>16,17</sup> but not yet in humans. Studies suggest that CBD reduces anxiety in patients with social phobia,<sup>18,19</sup> but this research did not include repeated dosing or patients with other diagnoses. The effect of CBD on sleep is largely unknown. One small study indicated that 160 mg of CBD helped with insomnia,<sup>20</sup> although another study showed no difference between CBD (300 mg) and placebo with respect to sleep.<sup>21</sup> Currently, CBD's only medical indication is childhood epilepsy,<sup>11</sup> for which Epidiolex (a CBD plant extract) is FDA-approved.<sup>22</sup>

Thus, our participants reported using cannabis for pain, anxiety, sleep, and nausea/vomiting, and this is largely supported by the research. However, our participants also reported using a wide range of THC and CBD products. Although THC has been shown to address pain, anxiety, insomnia, and nausea/vomiting, the effect of CBD on these symptoms is currently unknown.

#### Cannabis Use During Treatment

In our study, 79% of cannabis users reported taking it during active treatment, including cytotoxic chemotherapy, hormonal/immune therapies, radiation therapy, and surgery; this finding is similar to the findings of previous studies.<sup>8,23</sup> Additionally, 49% of medical cannabis users believed that cannabis could be used to treat cancer. However, concurrent use of cannabis with anticancer therapies raises important efficacy and safety concerns.<sup>24</sup> Many chemotherapy agents as well as cannabinoids are metabolized in the liver's p450 cytochrome system. The mechanism by which THC and CBD interact with particular CYP450 isoenzymes has the potential to alter the metabolism of other medications and lead to adverse side effects. For example, both THC and CBD competitively inhibit CYP3A, which is the isoenzyme responsible for metabolizing more than 60% of medications.<sup>25</sup> This includes several drug classes that are commonly used as adjunct therapies in the management of patients with cancer, such as antihistamines, azole antifungals, macrolides, and benzodiazipines.<sup>11,26,27</sup> It is important to note, however, that much of the drug-interaction data regarding cannabinoids is based on in vitro studies; therefore, clinical implications are still unknown. Furthermore, mechanisms of drug interactions also depend on the specific preparations

and the routes of administration. For example, a study evaluating the interaction of an herbal cannabinoid tea with irinotecan and docetaxel, 2 chemotherapeutic agents metabolized by CYP3A, showed no significant influence on the plasma pharmacokinetics of these drugs.<sup>28</sup> This highlights the need for ongoing clinical research regarding the use of cannabis in oncological patients.

Another concern is pulmonary toxicity from smoking or vaping cannabis during cancer treatment. Therapies such as CDK4/6 inhibitors and trastuzumab deruxtecan carry a significant risk of interstitial lung disease.<sup>29,30</sup> Additionally, breast radiation treatment fields often include a small volume of lung, and the mortality risk from radiotherapy is higher in tobacco smokers (5%) than nonsmokers (0.5%).<sup>31</sup> Although the research has not shown a conclusive link between smoking cannabis and chronic obstructive pulmonary disease and cancer (lung, head or neck),<sup>12</sup> it is not known whether inhalational cannabis has an impact on these cancer treatments. Nonetheless, an awareness of these risks is important for clinicians and patients.

Two recent studies reported reduced tumor response rates and survival in patients with advanced cancer who were using cannabis while receiving checkpoint inhibitors.<sup>32,33</sup> However, the patient groups were heterogeneous with respect to cancer types, organ involvement, and prior treatments. Nonetheless, in light of preclinical studies suggesting that cannabis has immunosuppressive effects, cannabis use among patients receiving immunotherapy should be regarded with great caution.<sup>34</sup> Additionally, preclinical studies have shown an interaction between the endocannabinoid system and hormone receptors, and this raises concerns regarding the impact of cannabis on the safety and efficacy of frequently used hormonal therapies.<sup>35</sup>

At present, preclinical studies show that THC and CBD reduce tumor growth and metastases in animal models of breast cancer.<sup>36</sup> However, it is not known whether this translates to human research. Despite the high level of interest in cannabis for its possible anticancer effects, at this point, the impact of cannabis on breast cancer treatment and breast cancer tumor burden remains unknown.

#### Sources of Cannabis and Perceived Safety

Participants reported using a wide range of products, including edibles, liquids/tinctures, and smoked/vaped products. These were obtained from multiple sources, which ranged from state-regulated dispensaries to "dealers" and family/friends. More than 70% of participants, including nonusers, felt that cannabis for medical purposes was safe. Approximately three-quarters of all participants believed that cannabis was better than "chemicals" and that the benefits outweighed the risks.

Despite participants' confidence in medical cannabis, most of our study participants were unclear on the differences between hemp and marijuana products. Furthermore, many of these products are unregulated, and this raises safety concerns. We review these issues here.

Cannabis products fall into 2 broad categories: 1) predominantly THC-containing and 2) predominantly CBD-containing. Products containing moderate/high THC levels are usually obtained from dispensaries (medical or recreational, depending on the state) or illegally (from family, friends, and "dealers"). Products containing moderate/high levels of CBD are usually derived from hemp (defined as a cannabis plant with <0.3% THC). Hemp products can be sold online or in stores, and they are less tightly regulated than marijuana-derived products obtained at dispensaries.

Most state-approved dispensaries require accurate labeling of THC and CBD content. However, most dispensaries carry products that predominantly contain THC rather than CBD. For example, only 20% of 196 products in 1 medical dispensary contained any CBD.<sup>37</sup> Thus, although the majority of our respondents preferred CBD-only and CBD-dominant products, these can be difficult to obtain from regulated sources. Nonlegal sources of cannabis tend to contain widely variable THC levels with negligible CBD content. A study of illegal cannabis showed a rise of THC levels from ~4% in 1995 to ~12% in 2014, whereas CBD levels fell from ~0.28% in 2001 to <0.15% in 2014.<sup>38</sup>

Cannabis product safety is a significant concern. State-regulated dispensaries usually test for product purity, although this varies across states. Patients using cannabis obtained from unregulated (usually illegal) sources run the risk of exposure to contaminants and pathogens. Studies and case reports show that unregulated cannabis may contain harmful pathogens (bacterial and fungal), heavy metals (cadmium, lead, magnesium, copper, and mercury), pesticides (insecticides and fungicides), and solvents.<sup>39,40</sup> Furthermore, e-cigarette or vaping-use lung injury is associated with e-cigarette products containing THC<sup>41,42</sup> and vitamin E acetate.<sup>43</sup>

Hemp-derived CBD products (containing <0.3% THC) are legal, but regulation of products purchased online or in stores is lacking, and this raises safety concerns. Recent publications show that 70% to 80% of retail CBD products are labeled incorrectly, and vaporization liquid has more labeling inaccuracies than oral preparations.<sup>44,45</sup> Notably, up to 25% of products tested contained significant levels of THC (contrary to the law and labeling), which could cause intoxication.<sup>44,45</sup>

Thus, there is a need for patients to be aware of the potential risks of cannabis products. The safest sources of THC cannabis products are state-approved medical dispensaries. However, these are not available on a wide-spread basis and usually require patients to obtain certification from an approved clinician. Furthermore, the price of cannabis obtained from a dispensary is generally higher in comparison with other sources.<sup>46</sup> This can drive patients toward illegal sources, but they should be aware of the risks of contaminants and pathogens. All patients should avoid vaping THC or CBD e-cigarettes.

Lastly, despite the common preference for CBD products, consumers should be aware of their inconsistent regulation, (including mislabeling of the CBD content and the potential for intoxication from unauthorized levels of THC). Relatively few CBD retailers provide a certificate of analysis documenting the cannabinoid content and testing for contaminants. Consumers should request a certificate of analysis when purchasing CBD products.

# Limitations

Our study is subject to inherent survey study limitations. Selection biases can result in the overrepresentation of cannabis users, symptomatic patients under treatment with more advanced disease, and residents of states with legalized cannabis.<sup>4,6</sup> Conversely, underreporting of cannabis use can result from its illegal status and social stigma. Recall bias can result in incomplete data on sources of information and patterns of use and blur distinctions between medical and recreational cannabis use. Access to our survey was limited because it was conducted only online and in English. In addition, the focus, scope, and length of the survey tool were constrained by the need to optimize survey participation, completion, and data quality; this limited our ability to gather important information about other important topics, such as cannabis use for purported anticancer effects. Data recall gaps, a lack of data verification with electronic medical and dispensary databases, and an absence of certificates of analysis for the products used also limited the accuracy and power of the survey data. Despite these limitations, our survey was able to capture a national sample of all age groups using a full range of medical therapies.

In conclusion, the literature overall shows that THC helps to treat pain and nausea, with some support

for insomnia and anxiety. Studies investigating CBD for these purposes are needed. Cannabis use during treatment is a significant concern because of limited data regarding potential interactions. Providers should communicate clearly about the health and safety concerns associated with certain cannabis products and methods of delivery. Without these measures, patients may make these decisions without qualified medical guidance, obtain poorquality cannabis products, and consume them through potentially hazardous delivery methods during various types of cancer therapies.

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#### CONFLICT OF INTEREST DISCLOSURES

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### AUTHOR CONTRIBUTIONS

Marisa C. Weiss: Development and implementation of the survey. Julianne E. Hibbs: Survey development. Meghan E. Buckley: Data analysis and preparation of the manuscript. Sherry R. Danese: Development and implementation of the survey. Adam Leitenberger: Survey development. Melissa Bollmann-Jenkins: Survey development. Sam W. Meske: Data analysis and preparation of the manuscript. Katherine E. Aliano-Ruiz: Data analysis and preparation of the manuscript. Theresa W. McHugh: Survey development. Sharon L. Larson: Data analysis and preparation of the manuscript. Nancye L. Green: Survey development. Paul B. Gilman: Data analysis and preparation of the manuscript. Virginia G. Kaklamani: Survey development. Rowan T. Chlebowski: Survey development. Diana M. Martinez: Development and implementation of the survey.

#### REFERENCES

- Berry DA, Cronin KA, Plevritis SK, et al. Effects of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353:1784-1792. doi:10.1056/NEJMoa050518
- Kahn O, Tilley D, Veitch Z, et al. Impact of cumulative chemotherapy dose on survival with adjuvant FEC-D chemotherapy for breast cancer. J Natl Compr Canc Netw. 2019;17:957-967. doi:10.6004/ jnccn.2019.7286

- Macari DM, Gbadamosi B, Jaiyesimi I, Gaikazian S. Medical cannabis in cancer patients: a survey of a community hematology oncology population. *Am J Clin Oncol.* 2020;43:636-639. doi:10.1097/COC.00000 00000000718
- Calcaterra SL, Burnett-Hartman AN, Powers JD, et al. A populationbased survey to assess the association between cannabis and quality of life amoung colorectal cancer survivors. *BMC Cancer.* 2020;20:373. doi:10.1186/s12885-020-06887-1
- Saadeh CE, Rustem DR. Medical marijuana use in a community cancer center. J Oncol Pract. 2018;14:e566-e578. doi:10.1200/JOP.18.00057
- Abrams D, Guzman M. Cannabis in cancer care. *Clin Pharmacol Ther*. 2015;97:575-586.
- Legal medical marijuana states and DC. ProCon.org. Updated May 28, 2021. Accessed June 8, 2021. https://medicalmarijuana.procon.org/ legal-medical-marijuana-states-and-dc/
- Pergram SA, Woodfield MC, Lee CM, et al. Cannabis use among patients at a comprehensive cancer center in a state with medicinal and recreational use. *Cancer*. 2017;123:4488-4497. doi:10.1002/ cncr.30879
- 9. Corroon J, Phillips JA. A cross-sectional study of cannabidiol users. *Cannabis Cannabinoid Res.* 2018;3:152-161. doi:10.1089/ can.2018.0006
- Braun IM, Wright A, Peteet J, et al. Medical oncologists' beliefs, practices, and knowledge regarding marijuana used therapeutically: a nationally representative survey study. *J Clin Oncol.* 2018;36:1957-1962. doi:10.1200/JCO.2017.76.1221
- Devinsky O, Cross JH, Wright S, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376:2011-2020. doi:10.1056/NEJMoa1611618
- National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies Press; 2017.
- Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313:2456-2473. doi:10.1001/jama.2015.6358
- Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2018;3:CD012182. doi:10.1002/14651858.CD012182. pub2
- Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6:995-1010. doi:10.1016/S2215-0366(19)30401-8
- 16. King KM, Myers AM, Soroka-Monzo A, et al. Single and combined effects of  $\Delta^9$ -tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. Br J Pharmacol. 2017;174:2832-2841. doi:10.1111/bph.13887
- Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. *Br J Pharmacol.* 2014;171:636-645. doi:10.1111/bph.12439
- Bergamaschi MM, Queiroz RHC, Chagas MCN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatmentnaïve social phobia patients. *Neuropsychopharmacology*. 2011;36:1219-1226. doi:10.1038/npp.2011.6
- Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol.* 2011;25:121-130. doi:10.1177/0269881110379283
- Carlini BH, Garrett SB, Carter GT. Medicinal cannabis: a survey among health care providers in Washington State. Am J Hosp Palliat Care. 2017;34:85-91. doi:10.1177/1049909115604669
- Linares IMP, Guimaraes FS, Eckeli A, et al. No acute effects of cannabidiol on the sleep-wake cycle of healthy subjects: a randomized, double-blind, placebo-controlled, crossover study. *Front Pharmacol.* 2018;9:315. doi:10.3389/fphar.2018.00315
- 22. FDA approves new indication for drug containing an active ingredient derived from cannabis to treat seizures in rare genetic disease. Food and Drug Administration. Published June 25, 2018. Updated March 27, 2020. Accessed March 19, 2021. https://www.fda.gov/news-event

s/press-announcements/fda-approves-new-indication-drug-containing -active-ingredient-derived-cannabis-treat-seizures-rare

- Martell K, Fairchild A, LeGerrier B, et al. Rates of cannabis use in patients with cancer. *Curr Oncol.* 2018;25:219-225. doi:10.3747/ co.25.3983
- 24. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clin Pharmacokinet*. 2016;55:1353-1368. doi:10.1007/s40262-016-0400-9
- Alsherbiny MA, Li CG. Medicinal cannabis—potential drug interactions. *Medicines (Basel)*. 2018;6:3. doi:10.3390/medicines6010003
- Foster BC, Abramovici H, Harris CS. Cannabis and cannabinoids: kinetics and interactions. *Am J Med.* 2019;132:1266-1270. doi:10.1016/j.amjmed.2019.05.017
- Finn K. Cannabis in Medicine: An Evidence -Based Approach. Springer Nature; 2020.
- Engels FK, Jong FA, Sparreboom A, et al. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist.* 2007;12:291-300. doi:10.1634/theoncologist.12-3-291
- Raschi E, Fusaroli M, Ardizzoni A, et al. Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. *Breast Cancer Res Treat*. 2021;186:219-227. doi:10.1007/s10549-020-06001-w
- Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610-621. doi:10.1056/NEJMoa1914510
- Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol.* 2017;35:1641-1649. doi:10.1200/JCO.2016.72.0722
- Bar-Sela G, Cohen I, Campisi-Pinto S, et al. Cannabis consumption used by cancer patients during immunotherapy correlates with poor clinical outcome. *Cancers (Basel)*. 2020;12:2447. doi:10.3390/cancers12092447
- Taha T, Meiri D, Talhamy S, Wollner M, Peer A, Bar-Sela G. Cannabis impacts tumor response rate to nivolumab in patients with advanced malignancies. *Oncologist.* 2019;24:549-554. doi:10.1634/theoncolog ist.2018-0383
- 34. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids:  $\Delta^9$ -tetrahydrocannabinol, cannabidiol and  $\Delta^9$ -tetrahydrocannabivarin. *Br J Pharmacol.* 2008;153:199-215. doi:10.1038/sj.bjp.0707442

- Dobovišek L, Krstanović F, Borštnar S, Debeljak N. Cannabinoids and hormone receptor–positive breast cancer treatment. *Cancers (Basel)*. 2020;12:525. doi:10.3390/cancers12030525
- Seltzer ES, Watters AK, MacKenzie D Jr, Granat LM, Zhang D. Cannabidiol (CBD) as a promising anti-cancer drug. *Cancers (Basel)*. 2020;12:3203. doi:10.3390/cancers12113203
- 37. Wilson-Poe A, Larsen E, Conan L, et al. Variability and paucity of medically relevant cannabis products in state regulated cannabis retail dispensaries. Paper presented at: 29th Annual Symposium of the International Research Cannabinoid Research Society; June 30, 2019; Bethesda, MD.
- ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. *Biol Psychiatry*. 2016;79:613-619. doi:10.1016/j.biopsych.2016.01.004
- Montoya Z, Conroy M, Heuvel BDV, Pauli CS, Park SH. Cannabis contaminants limit pharmacological use of cannabidiol. *Front Pharmacol.* 2020;11:571832. doi:10.3389/fphar.2020.571832
- Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370:2219-2227. doi:10.1056/NEJMra1402309
- Hartnett KP, Kite-Powell A, Patel MT, et al. Syndromic surveillance for e-cigarette, or vaping, product use-associated lung injury. N Engl J Med. 2020;382:766-772. doi:10.1056/NEJMsr1915313
- Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to ecigarette use in Illinois and Wisconsin—final report. N Engl J Med. 2020;382:903-916. doi:10.1056/NEJMoa1911614
- Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med. 2020;382:697-705. doi:10.1056/NEJMoa1916433
- 44. Gurley BJ, Murphy TP, Gul W, Walker LA, ElSohly M. Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the state of Mississippi. *J Diet Suppl.* 2020;17:599-607. doi:10.1080/19390211.2020.1766634
- Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318:1708-1709. doi:10.1001/jama.2017.11909
- Pacula RL, Smart R. Medical marijuana and marijuana legalization. *Annu Rev Clin Psychol.* 2017;13:397-419. doi:10.1146/annurev-clinp sy-032816-045128