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Does hyperbaric oxygen have a cancer-causing or -promoting effect? A review of the pertinent literature

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Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ, Sheffield PJ, Porter AT. Does hyperbaric oxygen have a cancer-causing or -promoting effect: a review of the pertinent literature. Undersea Hyperbaric Med 1994; 21(4):467–475.—We reviewed all known published reports or studies related to a possible cancer-causing or growth-enhancing effect by hyperbaric oxygen. Published articles were retrieved using Medline searches for the period 1960–1993. Additional references were obtained from bibliographies included in those articles discovered in the computer search. Also, hyperbaric medicine text books and the published proceedings of international hyperbaric conferences were visually searched. Studies and reports discovered in this fashion and related to the topic were included in the review. Twenty-four references were found: 12 were clinical reports, 11 were animal studies, and 1 reported both an animal study and a clinical report. Three clinical reports suggested a positive cancer growth enhancement, whereas 10 clinical reports showed no cancer growth enhancement. Two animal studies suggested a positive cancer-enhancing effect, and 10 animal studies showed no such effect. (The report that included both animals and humans is counted in both groups.) The vast majority of published reports show no cancer growth enhancement by HBO exposure. Those studies that do show growth enhancement are refuted by larger subsequent studies, are mixed studies, or are highly anecdotal. A review of published information fails to support a cancer-causing or growth-enhancing effect by HBO.

hyperbaric oxygen, cancer, human, animal, metastasis, carcinogenesis, free radicals, immune suppression

The first published concern that hyperbaric oxygen might have cancer-causing or cancer-enhancing properties appeared in a report by Johnson and Lauchlan in 1966 (1). These authors reported that an unusually high frequency and an unusual pattern of metastases were seen in women with advanced (stages III and IV) cervical cancer who had received HBO as a radiosensitizer. This publication was followed shortly thereafter by

additional clinical reports and animal studies that further investigated this issue. Reports addressing this concern continue to appear in the literature even in the 1990s.

A recent survey (2) of clinical hyperbaric facilities demonstrated that 7% of practicing hyperbaric physicians who responded to the questionnaire believed that HBO had carcinogenic potential. Fourteen percent of respondents believed that at least some of their referring physicians held this belief, and 42% of respondents believed they were at risk for malpractice litigation if a patient with a history of malignancy had a recurrence or acceleration of a tumor after a course of HBO.

Due to the failure of HBO-radiosensitized patients to show the anticipated improvement in local tumor control and disease-free survival, this practice has largely been abandoned (3). However, bony and soft tissue radiation necroses are UHMS-approved conditions for adjunctive HBO and a number of publications show a strong indication for HBO in this setting (4–6).

Inasmuch as about 50% of patients with a diagnosis of cancer will receive radiation at some time during their disease and HBO is efficacious in the treatment of late radiation complications, it would be useful to assess the risk of HBO as a cancer-causing or growth-enhancing agent. For these reasons, we have searched the medical literature to determine what support exists for concerns that HBO might activate or promote cancer growth or recurrence.

METHODS

A Medline computer search (English language from 1960 to 1993) was used to identify all publications that address the issue of cancer growth and recurrence. Bibliographies, book chapters, and the published proceedings of international hyperbaric medicine conferences were searched visually to locate additional references. From these sources, 24 pertinent reports were identified (1, 7–29). Twelve studies presented clinical results and another 11 reported animal studies; 1 additional publication reported both clinical and animal results. These studies are listed in Tables 1–4. Within each table, reports are listed in chronological order. Each table also details the general design of the study or report, including the protocol for hyperbaric exposures.

FINDINGS

Table 1 lists three clinical reports that suggest a positive cancer-causing or -promoting effect for HBO. Table 2 presents 10 clinical studies that are negative for cancer-causing or -promoting effects. Table 3 lists two animal studies that suggest a positive cancer-causing or -promoting effect for HBO, and Table 4 presents 10 references where the studies were negative for such effects. Note that Marx and Johnson (19) are listed in both Tables 2 and 4 because both clinical and animal results are presented by these authors.

Clinical reports are separated from animal studies. For each publication the design of the report and the number and depth of the HBO exposures are summarized in the appropriate table. Both primary tumor growth and metastatic growth are included because these were the details reported by the authors. Special attention was given to metastatic growth by most authors because the first anecdotal reports suggested that HBO might be affecting this aspect of the natural history of tumor progression. Also, metastatic growth was emphasized over primary growth because the primary growth in the clinical studies was usually attenuated by radiation therapy. In addition, primary tumor control was consis-

Table 1: Clinical Reports Suggesting a Cancer-Causing -Promoting Effect

Author	Year of Publication	Details of Report
Johnson, et al. (1)	1966	in 25 patients who were HBO radiosensitized with advanced cervical cancer, an unusual frequency and pattern of metastasis was seen; 30 HBO exposures, 3 atm abs
Cade, et al. (7)	1967	randomized controlled trial of 49 patients with bronchogenic CA and 40 with bladder CA. For bronchogenic CA rates of metastasis were the same as in HBO radiosensitized group, whereas for bladder HBO radiosensitized group had twice as many metastases; 40 HBO exposures, 3 atm abs
Eltorai, et al. (8)	1987	three cases of urothelial tumors (1 bladder; 2 urethra) had aggressive tumor growth after adjunctive HBO (highly anecdotal); 10–20 HBO exposures, 2 atm abs

tently improved in the HBO-sensitized groups, although not to the same extent as predicted by radiation biology principles. Among the clinical reports, squamous cell cancers of the head and neck and cervix were emphasized in the HBO radiosensitization trials. In these tumors, local control by radiation frequently equates to cure because they rarely produce hematogenous metastases.

Two of the three positive clinical studies come from early reports related to the effect of HBO used as a radiosensitizer. The third positive clinical publication is an anecdotal report of three patients with either bladder or urethral tumors who demonstrated an accelerated growth pattern after HBO. In toto, these studies include a total of 78 patients with either squamous cell or transitional cell malignancies.

Table 2 lists 10 negative clinical studies. Nine of these were trials intended to investigate whether HBO had utility as a radiosensitizer. One of the studies (11) was a larger, more mature study by the same author as the positive trial listed by Johnson (1). Also, the study by Perrins and Wiernik (15) is a larger trial of 236 patients related to HBO radiosensitization of bladder cancers. The positive study by Cade and McEwen (7) related to radiosensitizaton of bladder cancer included only 40 patients and was found to have a mismatch of stage and grade between the HBO and control groups, with more unfavorable patients assigned to the HBO group. Grade and stage of tumor are important determinants of prognosis in bladder cancer (30–32). The reports related to patients sensitized to radiation by HBO include squamous cell cancers of the head and neck, cervix, and lung as well as other bronchogenic cancer histologies, including adenocarcinomas and large cell cancers. Transitional cell cancers are also included in Perrins and Wiernik (15) and Dische (17).

The last entry in Table 2 by Marx and Johnson (19) reports their follow-up results of patients who received HBO for mandibular osteoradionecrosis in terms of tumor recurrence or second malignancies. All in all, Table 2 summarized the results of more than 2,000 patients exposed to HBO who were found to have no cancer growth enhancement.

Table 3 lists two animal trials where results suggest a positive effect of HBO on malignant growth. For spontaneous murine mammary tumors, Shewell and Thompson (20) reported an incident of 88.8% lung metastases in animals who received six HBO exposures at 2 atm abs compared to 66.6% in mice who were not exposed to HBO. In this report, a separate study of transplanted mammary tumors showed an identical incidence

Table 2: Clinical Reports Showing No Cancer-Initiating or -Promoting Effects

Author	Year of Publication	Details of Report
Van DenBrenk, et al. (9)	1967	85 head and neck patients with historic controls had statistically significant decrease in metastasis in HBO radiosensitized patients; 2–6 HBO exposures, 3 atm abs
Johnson, et al. (10)	1974	report of controlled trial of 64 cervical cancer patients; rates of metastasis same in HBO radiosensitized and control groups; 5-yr survival, 44% in HBO group vs. 16% in air; 25–30 HBO exposures, 3 atm abs
Henk, et al. (11)	1977	controlled trial of 276 patients with head and neck cancer; rates of metastasis same for HBO radiosensitized and air groups; recurrence-free survival better in HBO group; 10 HBO exposures, 3 atm abs
Henk, et al. (12)	1977	controlled trial of 104 patients with head and neck cancer; disease-free survival statistically improved in HBO radiosensitized patients; 10 HBO exposures, 3 atm abs
Bennett, et al. (13)	1977	report of a controlled trial of 213 patients with cervical cancer; no increase in metastases in HBO radiosensitized patients; 10 HBO exposures, 3 atm abs
Perrins, et al. (14)	1978	236 patients with bladder cancer randomized to radiation in air or HBO; no difference in survival to 4 yr and no difference in metastases; 6–40 HBO exposures, 3 atm abs
Watson, et al. (15)	1978	report of controlled trial involving 320 cases of cervical cancer; metastases virtually identical in HBO radiosensitized; 6–27 HBO exposures, 3 atm abs
Dische (16)	1979	report of controlled trial involving 1,500 patients with head and neck, bladder, bronchus, or cervical cancer; no increased metastases in HBO radiosensitized patients; 6–12 HBO exposures, 3 atm abs
Brady, et al. (17)	1981	report of controlled trial of 65 cases of cervical cancer; distant failure higher in control group (34%) vs. HBO sensitized group (16%); 10 HBO exposures, 3 atm abs
Marx and Johnson (18)	1988	reports 16.5% new tumors or local recurrence in patients after adjunctive HBO vs. 25% historic controls matched for stage; 20–40 HBO exposures, 2.4 atm abs

of lung metastases in HBO and control animals. The study by McMillan et al. (21) showed fewer but larger tumors in hamsters whose cheek pouches were exposed to dinitromethylbenzanthracene (DMBA) and HBO vs. control animals exposed to DMBA only.

Table 4 details the results of 10 negative animal studies. All were controlled trials where the end point was either transplanted primary growth, size and number of metastases, or survival. Histologies of transplanted tumors include adenocarcinoma (mammary tumors), melanoma, leukemia, carcinosarcoma, rhabdomyosarcoma, and squamous cell cancers.

Table 3: Animal Studies Suggesting Cancer-Causing or -Promoting Effects

Author	Year of Publication	Details of Report
Shewell and Thompson (19)	1980	two separate studies: transplanted and spontaneous murine mammary tumors; for spontaneous tumors 88.8% mets in HBO vs. 66.6% in air; otherwise primary tumor and mets in transplanted tumor identical; 6 HBO exposures, 2 atm abs
McMillan, et al. (20)	1989	DMBA-induced tumor in hamsters; HBO group had fewer tumors (3.56/animal) vs. air group (9.6/animal), but tumors were larger in HBO group 10.8 mm^2 vs. 3.5 mm^2 in air group; 85 HBO exposures, 2.5 atm abs

COMMENT

The vast majority of the above studies fail to demonstrate a cancer-causing or growth-enhancing role for HBO. The clinical studies discovered in our search are mostly from an earlier time and their scientific method would probably not withstand a review by today's rigorous standards. Most clinical information comes indirectly from studies designed to investigate whether HBO had a role as a radiosensitizer. These studies were not designed to address the issue of whether HBO has a carcinogenic or a tumor growth-enhancing effect. However, beginning with Johnson's publication in 1966 (1), the radiation therapy and hyperbaric oxygen communities were aware of the importance of this issue. Such an interest is evidenced by the animal studies that are reported in Tables 3 and 4 and were specifically designed to determine the effect of HBO on experimental tumors. The HBO radiation sensitization trials have been criticized on many occasions due to poor design. Indeed, many inconsistencies of trial design are evident when one reviews these studies. The criticisms relate to inconsistencies in terms of the radiation dose, with some investigators giving daily standard radiation doses (180–200 cGy) and others giving a few large fractions. However, all of these trials were consistent in comparing a control group radiated in air to an HBO-sensitized group. With the exception of one study utilizing historical controls (10), these studies were both randomized and prospective in this regard. Those clinical studies that are positive are either supplanted by larger and more mature studies, or are themselves mixed studies, or are highly anecdotal. Seventy eight patients were included in positive studies, whereas those in negative studies number over 2,000.

Table 3 lists two positive animal studies. One is itself a mixed study and even its positive report of increased metastases from 66.6% to 88.8% comparing control to HBO-exposed animals does not reach statistical significance. The second positive study by McMillan et al. (21) is a mixed study and is matched by an identical study by Marx and Johnson (19) which showed no such positive effect.

Table 4 details a broad experience in transplanted or chemically induced tumors in rodents. Tumors included carcinomas, sarcomas, melanomas, and leukemias. All of these studies failed to show a cancer-causing or growth-enhancing influence by HBO. Outcome determinants for these studies were growth of the primary tumors, number and size of metastases, survival, or a combination of these features.

We believe that a review of all the discoverable literature related to HBO as a potential inducer or enhancer of malignant growth fails to demonstrate such an effect. Yet, a recent

Table 4: Animal Studies Showing No Cancer-Causing or -Enhancing Effects

Author	Year of Publication	Details of Report
McCredie, et al. (21)	1966	transplanted C3HBA mouse mammary tumor; no effect on primary or metastasis; 12 HBO exposures, 3 atm abs
Suit, et al. (22)	1966	transplanted strong A and BDF mouse mammary tumor; no effect on primary or metastasis; 27–30 HBO exposures, 4 atm abs
DeCosse and Rogers (23)	1966	transplanted mouse melanoma decrease in pulmonary metastases; no change primary growth; 7–12 HBO exposures, 2 atm abs
Johnson, et al. (24)	1967	transplanted mouse melanoma and leukemia; for melanoma, no increase in primary or size and number of metastases; for leukemia, no decrease in survival; 20 HBO exposures, 3 atm abs
Dettmer, et al. (25)	1968	transplanted rat carcinosarcoma; both primary and metastases decreased in HBO arm; 8–23 HBO exposures, 3 atm abs
Evans (26)	1969	chemically induced mouse skin cancer; same incidence of lung metastases; single HBO exposure, 2 atm abs
Feder, et al. (27)	1968	transplanted rhabdomyosarcoma in mice; metastases identical in HBO group; 20 HBO exposures, 3 atm abs
Johnson, et al. (28)	1971	transplanted lymphoblastic leukemia; no difference in survival, primary tumor growth, or metastases; 11 HBO exposures, 3 atm abs
Marx and Johnson (18)	1988	DMBA-induced SCCA in hamsters; delay of growth in HBO group; 20 HBO exposures, 2.4 atm abs
Headley, et al. (29)	1991	transplanted human SCCA xenografts in nude mice; no differnce in growth; 15 HBO exposures, 2.4 atm abs

survey of clinical HBO facilities demonstrated a continued concern by an identifiable minority of clinicians that HBO was cancer causing or promoting. We should remember that second malignancies in cancer patients are not uncommon, especially in head and neck cancers where this incidence may be as high as 40% (33, 34).

What are the putative mechanisms whereby HBO might exercise a carcinogenic or cancer growth-enhancing effect? They include the following:

1. by nourishing the tumor;
2. by causing immune suppression;
3. by causing toxicity mediated through free radical formation.

It is a natural concern that since HBO is often indicated as an adjunct to stimulate neovascularization and growth of healing tissues, it could do the same for malignant tissues. However, it has been known since Warburg's publication in the 1930s (35) that one characteristic that sets malignant tissues apart from benign tissues is a preference for anaerobic pathways of glycolysis, even in the presence of oxygen. For this reason, the simple addition of high concentration of molecular oxygen is unlikely to stimulate malignant growth by heightened metabolism.

Immune suppression is a powerful risk factor for malignancy, as demonstrated by the high incidence of cancer in organ transplant patients on long-term, continuous regimens of immune suppression (36, 37). HBO has been shown to be immunosuppressive in some animal trials. However, in human subjects Feldmeier et al. (38) showed no effect of HBO on immune competence when these subjects were exposed to 20 daily HBO treatments.

Concerns that HBO can cause toxicity due to a drastic increase in free radicals are also valid. Free radicals have been implicated as risk factors for a number of deleterious and degenerative conditions including cancer (39). Recent publications have shown that HBO does not increase the deleterious effects of free radical damage (40). Kaelin et al. (41) have shown a significant increase in the activity of the free radical scavenger superoxide dismutase in animals exposed to HBO. Such an enhancement of free radical scavenger activity may well be the dominant effect of HBO in this circumstance and deleterious free radical effects may actually decrease under HBO conditions. In a similar fashion and for similar reasons it has been postulated that HBO is contraindicated in ischemia reperfusion injuries where oxygen free radicals would enhance the reperfusion injury.

Oncologists are slowly unraveling the biochemistry and pathophysiology of carcinogenesis and metastasis. Both carcinogenesis and metastasis are complex, multistep processes (42–44). As a minimum, carcinogenesis requires the action of an initiator that alters DNA content of a target cell or cells and begins the carcinogenic insult. This initial insult must be coupled with the activity of one or more promotors. For a clinical cancer to develop, the activity of these promotors must be prolonged over time. The process of metastasis requires a "cascade" of events including angiogenesis, invasion of local tissues, adherence to and migration through vascular endothelium, movement to the target organ through the vasculature, and invasion and colonization of the target organ.

The effects of HBO on the individual steps of the above-outlined processes have not been studied. The bulk of the reports reviewed here took place long before our present understanding of the process of cancer causation and progression. However, we believe that the compilation of these studies in a single paper is useful in furthering our understanding of the effects of HBO on cancer growth and contend that the literature to date fails to make a convincing case for a cancer-causing or growth-enhancing effect of HBO.

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