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Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis

Abstract: Most observational studies show an association between melatonin and cancer in humans. We conducted a systematic review of randomized controlled trials (RCTs) of melatonin in solid tumor cancer patients and its effect on survival at 1 yr. With the aid of an information specialist, we searched 10 electronic databases from inception to October 2004. We included trials using melatonin as either sole treatment or as adjunct treatment. Prespecified criteria guided our assessment of trial quality. We conducted a meta-analysis using a random effects model. We included 10 RCTs published between 1992 and 2003 and included 643 patients. All trials included solid tumor cancers. All trials were conducted at the same hospital network, and were unblinded. Melatonin reduced the risk of death at 1 yr (relative risk: 0.66, 95% confidence interval: 0.59–0.73, $I^2 = 0\%$, heterogeneity $P \leq 0.56$). Effects were consistent across melatonin dose, and type of cancer. No severe adverse events were reported. The substantial reduction in risk of death, low adverse events reported and low costs related to this intervention suggest great potential for melatonin in treating cancer. Confirming the efficacy and safety of melatonin in cancer treatment will require completion of blinded, independently conducted RCTs.

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Introduction

Melatonin, an indolamine secreted from the pineal gland, follows a circadian rhythm determined both by its production and secretion [1]. Melatonin is associated with effects on sleep, mood, sexual maturation and reproduction, immune function, aging, and the antioxidative defense system [1, 2].

The association between melatonin levels and cancer progression has suggested to some that melatonin may be a modifier of cancer progression. The mechanisms by which melatonin may act in this way have not been fully elucidated. One of the potential mechanisms is the possibility that the hormone has antimitotic activity as a result of intranuclear downregulation of gene expression or through the inhibition of growth factor release and activity [3, 4]. There is also evidence to support the inhibition of solid cancer growth in vivo by suppressing tumor linoleic acid uptake and metabolism via a melatonin receptor-mediated mechanism [5, 6]. Other possible anti-cancer mechanisms include protection from oxidative damage [7], anti-angiogenic activity [8], anti-inflammatory activity [9], anticachectic properties [10, 11], and immunostimulation [1, 12].

Data on the relationship between melatonin and cancer in humans is somewhat conflicting, however the majority of reports show a positive action. Associations of low levels of melatonin with human cancer include breast cancer [13]; prostate cancer [14], and endometrial, lung, gastric, and colorectal cancers [4, 15]. In addition, there is evidence for the beneficial use of melatonin during chemotherapy [12, 16–19]. Claims include the potential for melatonin to attenuate damage to blood cells from both radiation therapy and chemotherapy [20, 21]. Moreover, melatonin may induce a decline in the frequency of chemotherapy-induced asthenia, stomatitis, cardiotoxicity, and neurotoxicity [12].

A number of clinical trials have addressed the impact of melatonin on solid tumors; as yet, however, there is no satisfactory synthesis of the data. We performed a systematic review and meta-analysis of the literature for all randomized controlled trials (RCTs) examining survival at 1 yr that involve the use of melatonin in the treatment of a variety of cancers.

Methods

Data selection

With the aid of an information specialist, we (EM, PW) searched the following databases independently, in duplicate (from inception to October 2004): AltHealthWatch, AMED, CancerLit, CinAhl, Cochrane Controlled Trials

Table 1. Study characteristics

Reference	Description of randomization	Allocation concealment	Blinding status	Placebo	Ethics/ informed consent	Source of funding	Intention to treat
26	Yes[a]	Yes[a]	Open	No	Yes[a]	Unfunded[a]	Yes
16	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	No
27	Yes[a]	Yes[a]	Open	No	Yes[a]	Unfunded[a]	Yes
32	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	No
30	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	Yes
28	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	Yes
31	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	Yes
19	Yes	Yes[a]	Open	No	Yes	Unfunded[a]	Yes
36	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	Yes
29	Yes[a]	Yes[a]	Open	No	Yes	Unfunded[a]	Yes

[a] Information obtained from communication with author.

Register (CENTRAL), MedLine, and EMBASE. To identify unpublished research, we searched http://www.clinicaltrials.gov, National Research Register (UK) and the Meta-Register. Searches were not limited by language. We additionally searched bibliographies of identified reviews and contacted experts in the field. The following search terms were used, but not limited to: 'melatonin,' 'pineal hormone,' 'cancer,' and 'random*'.

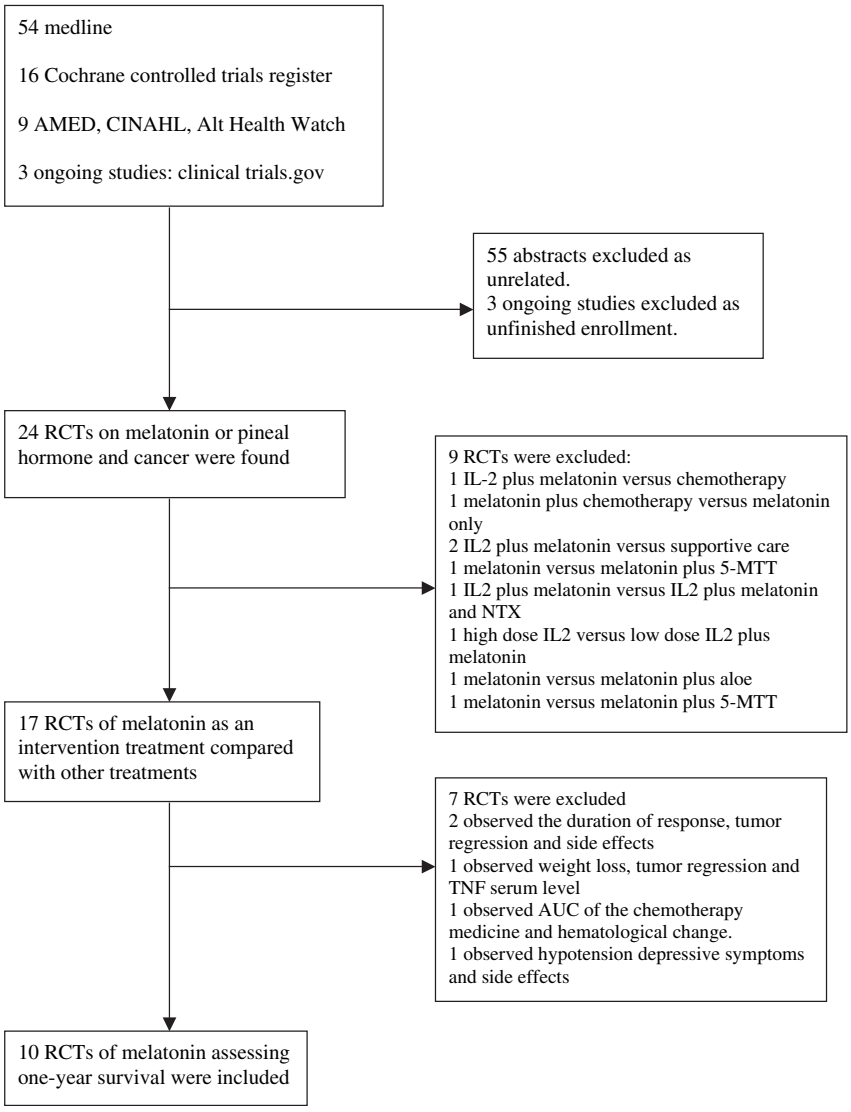

Fig. 1. Flow diagram of studies examined in this systematic review. 5-MTT, 5-methoxytryptamine; AUC, area under the curve; IL2, interleukin 2; NTX, naltrexone; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Table 2. Study findings

Reference	Population	n	Age range	Interventions	Outcomes measured	Dosage	ARR	NNT	RRR (95% CI)
26	Metastatic nonsmall cell lung cancer resistant to cisplatin	63	39–78	Melatonin versus supportive care	Progression Survival at 1 yr	10 mg/day orally at 19:00 hr	0.2	5	20% (3–40)
16	Brain metastases due to solid tumors	50	38–72	Supportive care + melatonin versus supportive care alone	Survival at 1 yr	20 mg/day at 20:00 hr	0.25	4	30% (3–53)
27	Advanced solid tumors other than renal cancer and melanoma	80	36–74	Interleukin 2 (IL2) + melatonin versus IL2 alone	Tumor regression Survival at 1 yr	40 mg/day orally at 20:00 hr	0.31	4	36% (15–55)
32	Breast cancer (ER−)	40	42–80	Tamoxifen + melatonin versus tamoxifen alone	Clinical response Survival at 1 yr Toxicity	20 mg/day at noon and 20 mg/day in evening	0.39	3	52% (14–76)
30	Brain glioblastoma	30	32–76	Radiotherapy + melatonin versus radiotherapy alone	Progression free survival Survival at 1 yr	20 mg/day	0.37	3	40% (9–46)
28	Malignant melanoma	30	38–81	No treatment versus melatonin	Lymph node relapse Disease free survival Survival at 1 yr	20 mg/day orally in the evening	0.4	3	38.5% (9–84)
31	Advanced nonsmall cell lung cancer	70	39–80	Cisplatin + etoposide + melatonin versus cisplatin + etoposide	Tumor regression Survival at 1 yr	20 mg/day orally in the evening	0.25	4	30.5% (4–52)
19	Advanced metastatic solid tumors	250	39–81	Chemotherapy + melatonin versus chemotherapy alone	Disease progression Survival at 1 yr	20 mg/day orally	0.28	4	36% (22–49)
36	Renal cell cancer	30	28–63	Morphine + melatonin versus morphine alone	Tumor regression Survival to 3 yr	20 mg/day orally in evening	0.29	4	57% (−17–86)
29	Metastatic nonsmall cell lung cancer	100	38–81	Chemotherapy + melatonin versus chemotherapy alone	Disease progression Survival to 5 yr Toxicity	20 mg/day orally in evening	0.37	3	47% (16–63)

ARR, absolute risk reduction; NNT, number needed to treat; RRR, relative risk reduction.

Inclusion and exclusion criteria

We include RCTs enrolling participants with diagnosed cancers and providing details of survival at 1 yr. We included trials involving patients of any age, sex, or cancer stage. We included trials using melatonin as either sole treatment and as adjunct treatment. Trials had to treat randomized patients equally with the exception that the active group receive melatonin.

We excluded animal studies, pharmacokinetic trials, and trials comparing melatonin when combined with other anti-cancer agents aside from standard chemotherapy regimens.

Data abstraction

EM, PW and DS developed and piloted data abstraction forms. EM and PW extracted data independently and in duplicate [22].

Quality assessment

Table 1 presents our assessment of trial quality. We determined methods of randomization, allocation concealment, blinding status of patients and assessors, use of placebo, ethics review and informed consent, sources of funding and adherence to the intention-to-treat principle. We contacted the study authors to determine items that were inappropriately reported.

Quality assessment and trial inclusion was performed independently, in duplicate (EM, PW) with third party arbitration when uncertainty existed (DS). We did not rely exclusively on the published reports of the trials as, in this case, the authors did perform important methodological criteria in the conduct of the trial, but did not report it in the original manuscript.

Statistical analysis

The kappa (κ) value provided a measure of chance-corrected agreement between assessors of eligibility and study quality. We determined the proportion of patients in treatment and control groups alive at 1 yr [23], the relative risks (RR) and applicable 95% confidence intervals (95% CI), the absolute risk reductions and numbers needed to treat (NNT) were determined. Pooled analysis of RR was conducted using a random effects model. We pooled the results of different trials for different cancers because the similar putative mechanism of action in each cancer suggests the possibility of similarity of response. We tested for homogeneity using the Zalen test and the I^2 test [24]. A priori explanations of heterogeneity included cancer type, dosage of melatonin and adjunct chemotherapy used. Publication bias was tested using both the Egger test with funnel plot and Kendall's test on standardized effect versus variance. In order to examine the temporal relationship of the accumulated data, we conducted a cumulative meta-analysis [25]. StatsDirect was used for all meta-analytic procedures (StatsDirect, Copyright 1993–2004, Manchester). We conducted both standard and cumulative meta-analyses.

Results

Fig. 1 details the yield of the sources and the study selection. κ for initial decisions on the inclusion of studies was 0.9 (95% CI: 0.6–1) suggesting excellent agreement. The 10 studies included (Table 2) were published between 1992 and 2003 and included 643 patients [16, 19, 26–32]. The included studies were all reported in English and were all from Italy and Poland. We additionally located two trials currently enrolling participants in the US (one trial for nonsmall cell lung cancer conducted by the Cancer Treatment Centers of America [33], and one for brain metastases by the National Cancer Institute [34]).

Determination of study quality (Table 1) indicates that the studies were of moderate quality, but lacked important methodological techniques shown to potentially prevent bias such as blinding and use of placebo. General reporting of the studies was poor, but contact with the studies' lead author clarified the missing information. All trials were hospital funded.

There is a suggestion of publication bias evident in the funnel plot [Eggers test: −1.260231 (approximate 95% CI: −2.508723 to −0.011738), $P = 0.0483$, Fig. 2). Kendall's tau had too small a sample size to conduct a robust evaluation, yet our extensive searches and contact with investigators suggest that no further trials have been conducted. The pooled RR, using a random effects model for conservative application is 0.66 (95% CI: 0.59–0.73, $P \leq 0.0001$) (Fig. 3). We did not detect significant statistical heterogeneity ($P = 0.568$, $I^2 = 0\%$). Effects were consistent across tumor type and dose of melatonin. Authors reported no severe adverse events and reported that melatonin was well tolerated in all trials. Fig. 4 displays the cumulative meta-analysis of the trials.

Discussion

Our meta-analysis indicates a consistent effect on 1-yr survival of adjunct melatonin in a variety of advanced stage cancers. In many cases the cancers that were being treated

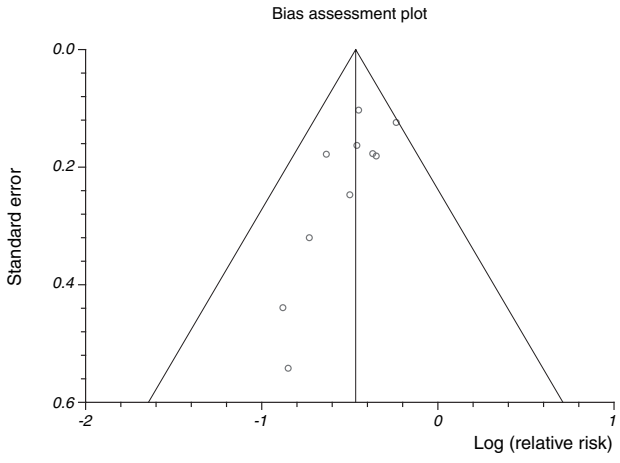

Fig. 2. Funnel plot: Eggers test: −1.260231 (approximate 95% CI = −2.508723 to −0.011738) $P = 0.0483$), Kendall's tau had too small a sample size to conduct a robust evaluation.

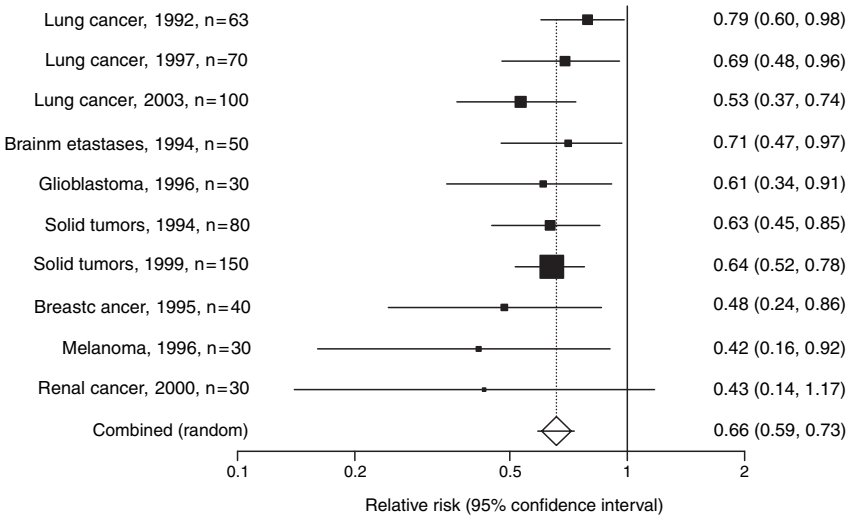

Fig. 3. Relative risk meta-analysis of 10 RCTs in various cancers using the random effects model.

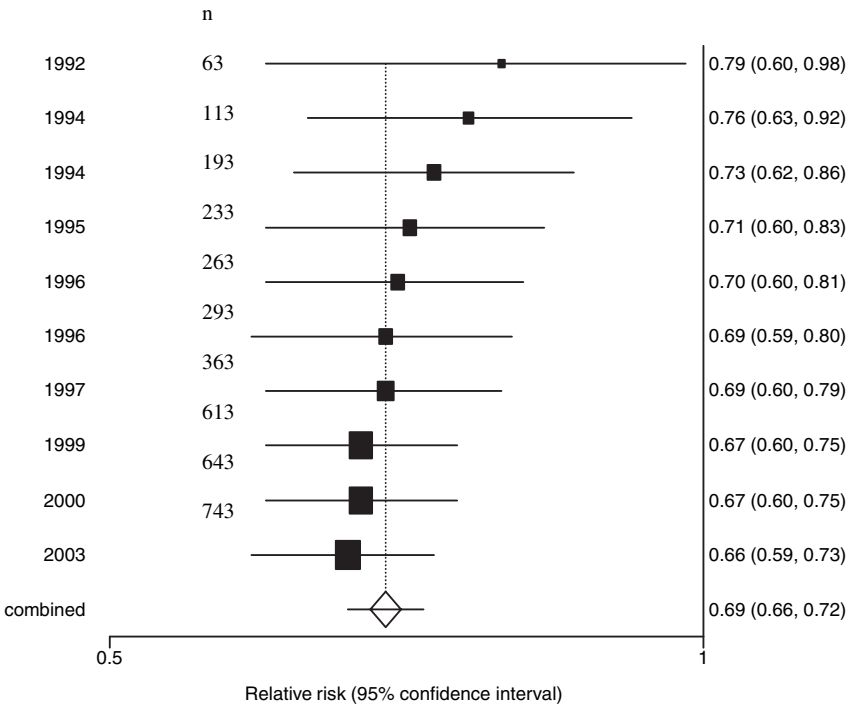

Fig. 4. Cumulative meta-analysis of 10 trials from 1992–2003.

were refractory to standard therapy and as such more amenable to the adjunct use of an untested and unproven therapy like melatonin. The pooled RR was 0.66 (95% CI: 0.59–0.73). The large effect size and low number of serious adverse events should be of interest to clinicians and patients.

There are several strengths to our meta-analysis: we conducted systematic searches of databases and contacted experts in the field to identify all RCTs available; we searched, abstracted and analyzed all data independently and in duplicate; we evaluated important methodologic criteria shown to influence trial outcomes; we contacted the authors of the trials to clarify trial conduct; and we conducted both standard and cumulative meta-analyses to determine at what point investigators might reasonably begin external trials to verify these findings.

There are several limitations to be considered in the interpretation of our meta-analysis. Perhaps the most significant is that the same network of investigators in Italy and Poland conducted all 10 trials. While this will not necessarily bias the results, the lack of independent verification, particularly in the presence of an effect that is perhaps surprisingly large, warrants skepticism. The funded Cancer treatment centers of America (CTCA) and National Cancer Institute (NCI) trials that are currently underway will begin to address this concern. Nevertheless, the cumulative meta-analysis suggests that evidence indicating the need for externally conducted trials has been available since 1992 (Fig. 4).

An additional concern is the methodological limitations of the study, particularly the lack of blinding. While all trials were limited in their original publication reporting,

contact with the lead author revealed that these trials were conducted using standard methods of enrollment, sequence generation and analysis. This finding is consistent with systematic evaluations of what is reported in trials compared with what was actually done [35].

The 20–40 mg dosage of melatonin shown to be effective in reducing the risk of cancer is much higher than the 1.5–5 mg used for the treatment of insomnia and jet lag. This raises the question of toxicity and whether or not there are significant side effects at these higher levels of intake. Generally, melatonin is considered relatively innocuous even at high doses, and the trials from Italy and Poland reported no significant side effects [18, 30, 31, 36–38]. One of the likeliest side effects of melatonin is the tendency to produce sedation or sleepiness in some people. While melatonin's antioxidant activity is not related to the time of day, to reduce the effect of sedation, melatonin is generally administered in the evening.

An article reviewing the safety of melatonin explored 307 articles of which nine were related to melatonin's adverse effects. The range of melatonin dosage involved in the adverse reactions spanned between 1 and 36 mg. The adverse reactions were not necessarily related to melatonin usage and were relatively rare; they included one patient with autoimmune hepatitis, one case of confusion caused by melatonin overdose, one case of optic neuropathy, four patients with fragmented sleep, one psychotic episode, one case of nystagmus, four cases of seizures, one case of headache and two cases of skin eruptions [39]. In addition, there is no long-term data on the safety of ingesting high levels of melatonin and it is possible that some adverse effects may not be realized in the short term [40]. It should be noted however that there has been widespread usage of over-the-counter melatonin with little indication of post-marketing toxicity.

In summary, this is the first meta-analysis examining the impact of melatonin on various cancers. This shows a strong association. The small NNT (range 3–5), low adverse events reported and low costs related to this intervention should be of substantial interest to patients, physicians and policy makers. Completion of independently conducted studies is required to confirm the efficacy and safety of melatonin in cancer treatment.

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