PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

Article

Prevalence of pharmacological control of arterial hypertension by ambulatory blood pressure measurement (ABPM) findings

José Abreu[1], Ramón Romano[2], Laura Reyes[3], Sharon Calderato[3], Oscar Vásquez[3], Pedro Peguero[3], Isabella Gutiérrez[3], Yaris Feliz[3]

[1]Instituto Tecnológico de Santo Domingo (INTEC), Centro Diagnóstico Especializado (CEDISA); [2]Instituto Tecnológico de Santo Domingo (INTEC), Harvard T.H. Chan School of Public Health, Centro de Diagnóstico Medicina Avanzada y Telemedicina (CEDIMAT); [3]Instituto Tecnológico de Santo Domingo (INTEC)

* *Correspondence: Ramón Romano, anthonyromanop@icloud.com*

Received: 08/15/2022; accepted: 12/15/2022; published: 04/04/2023.

ABSTRACT:

Introduction: Arterial hypertension (AHT) is one of the most prevalent chronic non-transmittable diseases and the main cause of cardiovascular death worldwide (World Health Organization, 2021). Adequate control of blood pressure levels is the best therapeutic measure to manage and prevent hypertension-related complications. In the Dominican Republic, there is insufficient and unreliable data related to pharmacological control through ambulatory blood pressure measurement (ABPM).

Methods: Cross-sectional and retrospective study, in which the results of 380 patients, who underwent an ABPM, were analyzed to determine if their blood pressure levels were within therapeutic control. The study was conducted between March 2022 and May 2022. The diagnostic criteria to determine blood pressure control were used from the guidelines of the Specialized Diagnostic Center (CEDISA), and included being older than 18 and having a study duration longer than 18 hours. Likewise, we excluded pregnant patients, patients diagnosed with heart failure, or patients taking triple antihypertensive therapy. For the data summary, we used mean and standard deviation. For statistical testing, we performed a Shapiro-Wilk normality test, and a two-tailed Student's t-test was used to assess the mean difference for which a value of $p<0.05$ was chosen to demonstrate significance. We performed a Bonferroni correction to adjust the significance value using the mean blood pressure in the repeated measures for the t-test, which reduced the significance from 0.05 to 0.016.

Results: The point prevalence of adequate pharmacological control was 44.2% (95% CI 39.21% to 49.19%). The mean systolic blood pressure of controlled patients was 117.8 (±7.5), while that of uncontrolled patients was 140.8 (±14.5). Between controlled and uncontrolled patients, the drugs most frequently used for managing hypertension were angiotensin II, receptor antagonists. There is a statistically significant difference between the mean 24-hour and daytime systolic blood pressure between males and females (p. 0.0016 and p. 0.0007, respectively) and 24-hour, daytime, and nighttime systolic blood pressure between controlled and uncontrolled patients (p. 0.000, p. 0.000, p 0.000, respectively)

Discussion: The prevalence of adequate pharmacological control in patients suffering from arterial hypertension encompasses 168 patients of the 380 studied, so it is evident that the remaining 212 patients, even when diagnosed, have not managed to obtain controlled blood pressure levels. The study was limited by not being able to investigate the treatment specifications and other risk factors.

Academic Editor: Felipe Fregni
Peer-reviewers: Cristina Bothou; Maria-Jose Hernandez-Woodbine.

Regardless of these issues, the study obtained the desired sample size; therefore, it can establish the study's reported AHT control prevalence as a direct measure of hypertensive patients in the Dominican Republic not being adequately controlled.

Keywords: arterial hypertension, prevalence, pharmacological control, ABPM, continuous measurement

DOI: http://dx.doi.org/10.21801/ppcrj.2022.84.5

Abbreviations:

(ABPM): Ambulatory blood pressure measurement
(ACC): American College of Cardiology
(ACEi): Angiotensin-converting enzyme inhibitor
(AHA): American Heart Association
(AHT): Arterial hypertension
(ARA II): Angiotensin II receptor antagonists
(ARBs): Angiotensin II receptor blockers
(BB): Beta-blockers
(BP): Blood pressure
(CCA): Complete Case Analysis
(CCB): Calcium channel blockers
(CEDISA): Specialized Diagnostic Center
(EFRICARD II): Cardiovascular Risk Factors and Metabolic Syndrome study in the Dominican Republic (translated from Spanish)
(ESC): European Society of Cardiology
(ENPREFAR-HAS): National Plan for Non-transmissible Diseases (translated from Spanish)
(INTEC): Instituto Tecnológico de Santo Domingo
(MCAR): Missing Completely at Random
(SD): Standard desviation
(STROBE): Strengthening the Reporting of Observational Studies in Epidemiology

Introduction

Arterial hypertension (AHT) is one of the most prevalent chronic non-transmittable diseases, and the leading cause of cardiovascular death worldwide (World Health Organization, 2021). It is estimated that the worldwide prevalence of AHT encompasses 26% of the world's population, projecting an increase of 29% by 2025 (R. Alexander, 2019). This can be attributed to patients' inability to have adequately controlled blood pressure (World Health Organization, 2021) (Basile & J Bloch, 2021).

Statistical data on AHT vary due to changes in clinical diagnostic guidelines. Therefore, there are systemic differences between the prevalence of parameters worldwide; during the revision of the guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC), in 2017, an increase in AHT prevalence was recorded: from 41.7% between 2013 and 2014 to 45.4% from 2017 to 2018 (Basile & J Bloch, 2021) (M. Egan, 2021).

In the Dominican Republic, the National Plan for Non-transmissible Diseases (ENPREFAR-HAS) 2017 reported that 31% of Dominicans older than 18 suffered from AHT. Nevertheless, the Cardiovascular Risk Factors and Metabolic Syndrome study in the Dominican Republic (EFRICARD II) reported a prevalence of 44% and an even higher percentage between the ages of 20 to 40 (Pichardo, 2012). Likewise, the Dominican Society of Cardiology and National Insurance of Health reported a study of 2,016 patients, of which only 36% were controlled (Perez Rubiera, 2020).

Additionally, a study reported that the AHT prevalence in 1,085 men and 1,183 women was 29.3%, which means 665 were hypertensive patients. Of the 665, 68.6% knew their condition and 54% were undergoing pharmacological treatment; of those who remained with controlled blood pressure, 33% were men and 49% were women (Marron, 2011).

The Dominican Institute of Cardiology published an article titled "Arterial Hypertension Management Profile According to Comorbidities". They concluded that the most frequent form of treatment was monotherapy, as an angiotensin-converting enzyme inhibitor (ACEi). For controlled patients, the most applied combination was ACEi with beta-blockers (BB). For uncontrolled patients, the most used drug was a single dose of beta-blockers. The most used combination in this group was angiotensin II receptor antagonists (ARA II) with BB (Cuello De Los Santos & Tavarez & Reyes, 2017).

In the Dominican Republic, there isn't sufficient and reliable data related to the pharmacological control of blood pressure in hypertensive patients. Even so, AHT data have not been reported through the use of a follow-up measurement ABPM. Therefore, there is no sufficient information to assess its current prevalence, associations, or sociodemographic characteristics to evaluate countermeasures as part of a public health issue.

Because of this, we proposed to carry out a cross-sectional study of hypertensive patients who have undergone ABPM, to monitor blood pressure control, and thus, answer the clinical question: In patients over 18 years old diagnosed with arterial hypertension, what is the prevalence of adequate control of hypertension with pharmacological therapy, measured through ambulatory blood pressure monitoring (ABPM) over 24 hours?

This question encompasses specific objectives such as describing the characteristics of the study population and testing for mean differences between sex, controlled and uncontrolled patients according to the results of the preceding ABPM.nce and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references.

Materials and Methods

Study design

This was a cross-sectional and retrospective study. The investigation was reported under the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Patients were assessed for adequate control of their blood pressure while taking antihypertensive medication, using ABPM as a 24-hour measure of their blood pressure.

Study Setting

The study was carried out at Centro Diagnóstico Especializado (CEDISA), in Santo Domingo, Dominican Republic. The proposal was approved by Proyecto BioINTEC, a research project committee of Instituto Tecnológico de Santo Domingo (INTEC), and later submitted to be reviewed by CEDISA in March 2022. The data collection process began after the proposal's approval in mid-March 2022. The days on which ABPM measurement cuffs were placed were Monday, Wednesday, and Friday; and on Tuesday and Thursday, the patient's results were processed by an on-call cardiologist and reviewed by one of the researchers assigned to the study. The data collection process ended on May 31st, 2022, with 380 patients.

Participants

The patients that were part of the study were selected through a convenience sampling technique. Patients 18 or older, undergoing ABPM to assess their pharmacological therapy, to determine if the patients were adequately controlled, were eligible. Patients who were pregnant, suffered from heart failure, had incomplete data collection forms, insufficient monitoring duration (<18 hours), triple antihypertensive therapy, or prolonged monitoring (>48 hours) were excluded.

Variables

The main outcome of the study was to assess the point prevalence of adequately controlled hypertension, by measuring the 24-hour mean of both systolic and diastolic blood pressure. Also, diurnal and nocturnal means of both systolic and diastolic blood pressure were measured. These variables were treated as continuous variables.

Other measurements included socio-demographic information, treatment combinations, and past medical history.

Possible confounders to these measures include past medical history not adequately documented in the patient's files, and any activity during the day that might've affected the study's results. Also, the patient's different baseline characteristics regarding any difference that could not be detected during the statistical analysis.

The interpretation parameters are based on the recommendations of the guidelines of the European Society of Cardiology (ESC) and Arterial Hypertension, updated in 2018.

That said, determining controlled arterial hypertension, is done according to 3 measurements: mean daytime blood pressure (systolic blood pressure < 135 mmHg, diastolic blood pressure < 85 mmHg), mean nighttime blood pressure (systolic blood pressure < 120 mmHg, diastolic blood pressure < 70 mmHg), and 24-hour mean blood pressure (systolic blood pressure < 130 mmHg, diastolic blood pressure < 80 mmHg).

The ABPM results are validated as uncontrolled hypertension when any of the following arises: the mean daytime blood pressure is >135/85 mmHg, the mean nighttime blood pressure is >120/70 mmHg, or the 24-hour mean blood pressure is > 130/80mmHg.

Data sources/measurement

Studies in which ≥ 60% of schedules were valid for the study. The ABPM monitors used by CEDISA are accredited in the "British and Irish Hypertension Society" lists.

By procedure protocol, patients were instructed not to engage in stressful activities, including exercise routines, forced labor, or any event that may directly interfere with the device that may alter the interpretation of the study. Also, not to perform or be part of stressful situations that could evoke anxiousness.

The data collection process began with the patients under HTA treatment. This involved the application of a questionnaire that covered

sociodemographic data. This form is a tool of CEDISA. It measured the variables: sex, age, comorbidities, current HTA medication, and the mean diurnal blood pressure, nocturnal blood pressure, mean 24-hour blood pressure, and night reduction percentage. The data was transferred from the form of CEDISA to computerized forms of the Kobotoolbox by doing a double check on every patient response. The collaborators proceeded to collect the necessary data, through the form of the patients attending the center, until the required number of patients, or 50% of the sample within the stipulated time (5 months).

Risk of Bias

Due to the nature of the data collection process, the study foresaw the possibility of confounding, the Hawthorne effect, and observer bias.

Regarding confounding, we could not perform any analysis or measures to avoid the intricacy that variables such as past medical history, prior exposure to strenuous physical activity or psychomotor stressors might've over the arterial pressure levels of the study participants.

Patients that might've been exposed to a certain degree of Hawthorne effect due to the physicians' presence during the initial interview, were re-assure of their answers to be given with the utmost honesty. This is because of their connection to their healthcare well-being. However, there isn't a measure to take into account to handle the Hawthorne effect.

When assessing the ABPM results, to handle observer bias, the results were double-checked by the cardiologist on-call and one of the researchers on-site, to reduce inter-rater variability.

Study size

For the required sample size, we used a Z score of 1.96, a confidence level of 95%, a margin of error of 5%, and a prevalence proportion of arterial hypertension of 44% (5). The results yielded a sample (n) of 379 patients. A non-probability convenience sampling technique was used to choose patients in the order of reporting results because they are directly proportioned according to their admission to the clinic.

Quantitative variables

Variables treated as continuous outcomes were age, mean blood pressure (daytime, nighttime, and 24-hour mean), and both systolic and diastolic. For analysis purposes, we categorized patients as controlled, uncontrolled, and whether they had monotherapy or dual therapy.

Statistical methods

For data collection and storage, we used the KoboToolBox tool. For tables, figures, and processes, Microsoft Excel 2017, and for statistical analysis, the STATA - BE program, version 17.

Concerning descriptive statistics, we summarized the quantitative data using the mean and standard deviation. And for qualitative data, we used frequency measures. We tested normality using Shapiro-Wilk's p-value for data distribution, with the variables age and mean blood pressure (daytime, nighttime, and 24 hours). We also added the standard errors for the mean blood pressure values with their standard deviation.

The measured prevalence rate of controlled patients used the number of controlled patients and the total patients at risk. These were used as numerators and denominators, respectively, as part of the main outcome. A pie chart was used to represent this.

A two-tailed t-test was used to test for differences in mean blood pressure between gender and between controlled and uncontrolled patients. The latter, to further validate the difference in the mean between each group

To represent the results of the other variables, we used table 1 of socio-demographic representation.

Regarding missing data, we used a Complete Case Analysis (CCA), for purposes of maintaining a complete data format. Following this, we excluded patients due to incomplete information during the data collection process, further prompting us to gather more patients, which meant we ended up having a sample size (n) of 380 with the exclusion of 22 patients.

In the appendix, there are supplementary documents related to ethical approval, the data collection questionnaire, and the ABPM form. Since the official documents cannot be translated into English, they were therefore attached in Spanish. Regarding the questionnaires, they were translated for a better understanding during the publication process.

Results

Descriptive data

From March through May 2022, a total of 380 patients were included in the study, out of that number, only 44.2% were in the controlled group based on the parameters as mentioned earlier.

The mean age was 55 years for controlled patients, and 56 for uncontrolled patients; as shown in Table 1, 66% of the participants were women. The most common comorbidity amongst the population was Diabetes Mellitus, which was present in 2.83% of the totality of the patients. The mean systolic blood pressure

	AHT status		P value
Demographic characteristics	**Controlled**	**Not controlled**	
Number of cases	168	212	
Sex (No. Of cases, %)			
Masculine	46 (27.38%)	82 (38.68%)	
Feminine	122 (72.62%)	130 (61.32%)	
Age (years ± SD)	55.36 ±13.29	56.43 ±14.59	
Personal medical history (No. Of cases, %)			
Diabetes mellitus	9 (2.37%)	2 (0.53%)	
Coronary artery disease	1 (0.26%)	0 (0.00%)	
Other	7 (1.84%)	2 (0.53%)	
Mean arterial blood pressure (mmHg ± SD)			
24 hr systolic	117.81 ±7.60	140.88 ±14.52	0.0000
24 hr diastolic	68.63 ±6.42	80.0.4 ±9.89	
Daytime systolic	121.50 ±8.34	143.45 ±15.53	0.0000
Daytime diastolic	71.59 ±7.22	82.27 ±10.64	
Nighttime systolic	108.61 ±7.38	134.19 ±15.54	0.0000
Nighttime diastolic	60.86 ±6.21	73.90 ±10.40	

Table 1. Demographic and clinical characteristics of the participants

during the 24 hours was 117.8 mmHg (±7/6) in controlled patients; for the non-controlled group, the mean value was 140.88 mmHg (±14/9).

A t-student test was used to compare the mean systolic blood pressure of the patients according to their AHT control status during the three periods. Statistical testing showed a significant statistical difference between both groups in each period (p. 0.000 for all 3 comparisons). This further validates the initial classification of their AHT control status.

Missing data

22 patients were excluded due to missing data: 20 had missing values related to mean systolic daytime data, and 2 had missing values in mean 24-hour systolic nocturnal data. This is further discussed in the limitations.

Main results

The results show that 44.2% (95% CI 39.21% to 49.19%) of the patients have controlled systolic arterial hypertension, corresponding to 168 of the evaluated subjects. On the other hand, 212 of the patients, corresponding to 55%, have uncontrolled systolic arterial hypertension.

A t-student test was used to compare gender to the means of systolic blood pressure (24 hours, daytime, and nighttime). Across the three periods, the mean systolic arterial pressure of the male patients was higher.

When comparing both groups at each mean systolic blood pressure, both the 24-hour mean and daytime mean showed significant statistical difference (p-value 0.0016, 0.0007, respectively), except for the nighttime mean systolic blood pressure with a p-value of 0.0349. The frequency of antihypertensive drugs was distributed more commonly towards monotherapy using ARBs (n=237), in both uncontrolled and

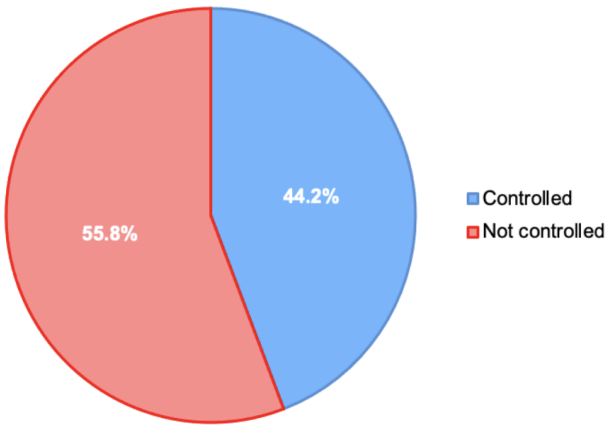

Figure 1. Prevalence of adequate pharmacological control of arterial hypertension

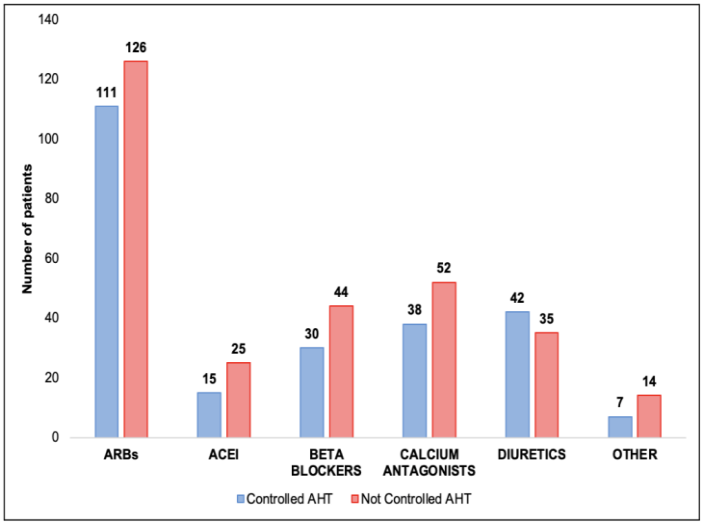

Figure 2. Distribution of patients according to drug combinations

controlled patients. Most uncontrolled patients had been using ARBs and calcium channel blockers (CCB) as primary therapy. For controlled patients, they were using ARBs and diuretics as primary therapy.

Discussion

Key results

The reported prevalence of adequately controlled AHT patients is 44.2% (95% CI 39.21% to 49.19%).

Most patients (both controlled and uncontrolled) used ARBs as monotherapy. Male patients had higher levels of mean systolic pressure during the 24-hour, daytime, and nighttime periods. However, only 24-hour and nighttime mean systolic pressure showed a statistical difference between their female counterparts.

Between sex, the majority of controlled and uncontrolled patients were females, which also showed that most patients (both male and female) were uncontrolled, in comparison to their controlled counterparts.

Arterial hypertension is the leading cause of cardiovascular burden worldwide (World Health Organization, 2021), and the main course of action to prevent, treat, and accurately control it is to gain useful data on AHT patients.

To our knowledge, this is the first study to assess pharmacological control of AHT patients in the Dominican Republic.

Limitations

The study's sample size of 379 patients, prompted the use of a sampling technique that allowed the research team to acquire the patients in the limited time frame, for which a convenience method was chosen. The resulting selection bias is evident in the sex distribution of the study: more women than men in each AHT control status group, thus the representativeness of the study is not as high as we would expect it to be.

Due to the use of the clinic's own sociodemographic and ABPM questionnaire, we couldn't add

Mean 24hr systolic BP							
Group	Obs	Mean	SE	SD	[99.9% CI]		*p-value*
Masculine	128	134.43	1.47	16.65	129.47	139.39	0.0016
Feminine	252	128.78	1.02	16.23	125.37	132.18	
Combined	380	130.68	0.85	16.56	127.86	133.50	
diff		5.65	1.78		-0.24	11.54	
Mean daytime systolic BP							
Group	Obs	Mean	SE	SD	[99.9% CI]		*p-value*
Masculine	128	137.84	1.54	17.40	132.65	143.02	0.0007
Feminine	252	131.67	1.02	16.21	128.27	135.07	
Combined	380	133.75	0.86	16.85	130.88	136.61	
diff		6.17	1.80		0.18	12.15	
Mean nighttime systolic BP							
Group	Obs	Mean	SE	SD	[99.9% CI]		*p-value*
Masculine	128	125.59	1.55	17.55	120.37	130.82	0.0349
Feminine	252	121.50	1.13	17.95	117.73	125.27	
Combined	380	122.88	0.92	17.90	119.83	125.92	
Diff		4.09	1.93		-2.32	10.51	

Table 2. Mean 24-hours, daytime, and nocturnal systolic blood pressure according to sex

more complementary questions to assess the whole demographic profile of the patients. Moreover, there's a clear reporting bias regarding the distribution of self-reported comorbidities, since most patients did not report any comorbidities or past medical history.

This could be explained by inherent behavior to avoid mentioning any ailments or simply avoid responding to them on the first encounter and mark the response as comorbidity-free. Regardless of the cause, it is impractical to determine the real cause.

Time constraints and first-week adjustment created systematic errors in the managing of the data inside the KoboToolBox framework, for which we had to exclude the first 22 patients due to missing data.

Due to the characteristics of the error made, we classified this as Missing Completely at Random (MCAR) data.

Interpretation

The prevalence of 44.2% (95% CI 39.21% to 49.19%) of adequately controlled patients, demonstrates a public health issue already described with similar readings of 48.2% (95% CI44.4–52.0) (Rana et al., 2020). To determine what conditions an adequate or inadequate control, several hypotheses could be tested: is it an economical issue? Whilst this study does not address economic disparities or socioeconomic status, it has been studied that adequate control is lower in low- and middle-income countries (Egan et al., 2022).

The data shown here is reason enough to further investigate the main factors affecting pharmacological control. However, to make inferences of target therapeutic goals for these patients is not possible with the current information; data regarding cardiovascular risk factors is needed (FE Mann, 2022). The inference of the study results only propels the need for more clinical research regarding the current overall cardiovascular and sociodemographic profile of these patients. Unfortunately, in the Dominican Republic, the report of cardiovascular research remains underestimated, as such, we can't add data to important trends and changes in what's currently happening with AHT prevalence and control: the coronavirus disease 2019 (COVID-19) pandemic, rates of hypertension control declined among adults in the United States, which could mean that it also happened in other areas worldwide (Egan et al., 2022).

Generalizability

There are clear similarities between reported age, gender, drug use distribution, and AHT control prevalence between this study and other works of literature (Zhou et al., 2021) (Tapela et al., 2021). This further explains a possible trend of distribution of men having worse rates of control than women, and not having changes across different economic backgrounds (Tapela et al., 2021). However, sampling bias might've decreased the external validity of the study, therefore its generalizability towards other key target populations needs to be evaluated carefully.

Regardless of these issues, the study was able to obtain the desired sample size, and the narrow CI can ascertain a certain degree of reproducibility of the study's findings of the reported AHT control prevalence to the main target population: hypertensive patients in the Dominican Republic, are not controlled.

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
Acknowledgments: Centro Especializado Diagnóstico (CEDISA) provided the ABPM machines to perform the study and ABPM cuffs.

References

Bijlsma, M. F., Spek, C. A., Zivkovic, D., van de Water, S., Rezaee, F., & Peppelenbosch, M. P. (2006). Repression of smoothened by patched-dependent (pro-)vitamin D3 secretion. PLoS Biol, 4(8), e232. doi:10.1371/journal.pbio.0040232

Burns, E. M., Elmets, C. A., & Yusuf, N. (2015). Vitamin D and skin cancer. Photochem Photobiol, 91(1), 201-209. doi:10.1111/php.12382

Christenson, L. J., Borrowman, T. A., Vachon, C. M., Tollefson, M. M., Otley, C. C., Weaver, A. L., & Roenigk, R. K. (2005). Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA, 294(6), 681-690. doi:10.1001/jama.294.6.681

Gould, A., & Missailidis, S. (2011). Targeting the hedgehog pathway: the development of cyclopamine and the development of anti-cancer drugs targeting the hedgehog pathway. Mini Rev Med Chem, 11(3), 200-213. doi: 10.2174/138955711795049871

Guy, G. P., Jr., Machlin, S. R., Ekwueme, D. U., & Yabroff, K. R. (2015). Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. Am J Prev Med, 48(2), 183-187. doi:10.1016/j.amepre.2014.08.036

Hahn, H., Wicking, C., Zaphiropoulous, P. G., Gailani, M. R., Shanley, S., Chidambaram, A., . . . Bale, A. E. (1996). Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell, 85(6), 841-851. doi: 10.1016/s0092-8674(00)81268-4

Jacob, L., & Lum, L. (2007). Hedgehog signaling pathway. Sci STKE, 2007(407), cm6. doi:10.1126/stke.4072007cm6

Karagas, M. R., Greenberg, E. R., Spencer, S. K., Stukel, T. A., & Mott, L. A. (1999). Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer, 81(4), 555-559. doi: 10.1002/(SICI)10970215(19990517)81:4%3C555::AID-IJC9%3E3.0.CO;2-R

Lomas, A., Leonardi-Bee, J., & Bath-Hextall, F. (2012). A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol, 166(5), 1069-1080. doi:10.1111/j.1365-2133.2012.10830.x

Marcil, I., & Stern, R. S. (2000). Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol, 136(12), 1524-1530. doi: 10.1001/archderm.136.12.1524

Reddy, K. K. (2013). Vitamin D level and basal cell carcinoma, squamous cell carcinoma, and melanoma risk. J Invest Dermatol, 133(3), 589-592. doi:10.1038/jid.2012.427

Rogers, H. W., Weinstock, M. A., Harris, A. R., Hinckley, M. R., Feldman, S. R., Fleischer, A. B., & Coldiron, B. M. (2010). Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol, 146(3), 283-287. doi:10.1001/archdermatol.2010.19

Sassi, F., Tamone, C., & D'Amelio, P. (2018). Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients, 10(11). doi:10.3390/nu10111656

Tang, J. Y., So, P. L., & Epstein, E. H., Jr. (2007). Novel Hedgehog pathway targets against basal cell carcinoma. Toxicol Appl Pharmacol, 224(3), 257-264. doi:10.1016/j.taap.2006.12.011

Tang, J. Y., Xiao, T. Z., Oda, Y., Chang, K. S., Shpall, E., Wu, A., . . . Epstein, E. H., Jr. (2011). Vitamin D3 inhibits hedgehog signaling and proliferation in murine Basal cell carcinomas. Cancer Prev Res (Phila), 4(5), 744-751. doi:10.1158/1940-6207.CAPR-10-0285

Telfer, N. R., Colver, G. B., Morton, C. A., & British Association of, D. (2008). Guidelines for the management of basal cell carcinoma. Br J Dermatol, 159(1), 35-48. doi:10.1111/j.1365-2133.2008.08666.x