Sunburn and malignant melanoma

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Abstract

Background: Unfortunately, despite recent scientific advances the cause of malignant melanoma is not identified. The incidence of malignant melanoma increases and malignant melanoma continues to represent a significant individual and public health challenge.

Objectives: In this systematic review studies were re-analyzed so that some new inferences can be drawn.

Statistical Analysis: The method of the conditio per quam relationship was used to proof the hypothesis whether the presence of human papillomavirus guarantees the presence of malignant melanoma. In other words, if human papillomavirus is present, then malignant melanoma is present too. The mathematical formula of the causal relationship k was used to proof the hypothesis, whether there is a cause effect relationship between human papillomavirus and malignant melanoma. Significance was indicated by a p-value of less than 0.05.

Results: The studies analyzed support the null-hypothesis that the presence of human papillomavirus guarantees the presence of malignant melanoma. In other words, human papillomavirus is a conditio per quam of malignant melanoma while the cause effect relationship between human papillomavirus and malignant melanoma was highly significant.

Conclusions: Human papillomavirus is a sufficient condition of malignant melanoma. Human papillomavirus is a cause of malignant melanoma.

Keywords: Human papillomavirus, malignant melanoma, cause effect relationship, causality

1. Introduction

The incidence of malignant melanoma (MM) around the world especially in indoor-working people is increasing (Merrill et al., 2015; Godar et al., 2009). Meanwhile, several potentially modifiable environmental risk factors (Kulichová et al., 2014; Rastrelli et al., 2014; Norval et al., 2017) for malignant melanoma (Bauer & Garbe, 2003) including exposure to ultraviolet (UV) radiation, high numbers of common naevi, large congenital naevi, multiple and/or atypical (Bauer) naevi (dysplastic naevi) have been discussed in literature. To date, it is generally agreed that UV sunlight exposure (Lancaster and Nelson, 1957; Ruttan, 1957; McGovern and Mackie, 1959; Setlow et al., 1993; Oikarinen & Raitio, 2000; Wang et al., 2001; Reichrath et al., 2014; Moan et al., 2014; Kulichová et al., 2014) and painful sunburns are the main etiologic agents in malignant melanoma. In point of fact, such and similar scientific positions supported by prevention campaigns of authorities resulted in a behavior for protection from UV radiation like avoiding sun exposure. The results from observational studies on the relationship between UV radiation and malignant melanoma disease remain controversial. Ironically, studies documented that the annual UV dose of out-door workers is 3–10 times greater (Godar, 2005) than that indoor workers. Yet out-door workers have lower incidences of MM (Kennedy et al., 2003; Gandini et al, 2005; Chang et al., 2009; Radespiel-Tröger et al., 2009) than indoor-workers. Furthermore, an excessive use of sunscreens which are able successfully to prevent sunburn did not result in a decrease in the incidence of MM (Vainio et al., 2000) but rather in a sunscreen dose-dependent increase in the incidence of MM (Westerdahl et al., 1995). An excessive use of sunscreens was not found to protect against malignant melanoma (Westerdahl et al., 1995). In the following, Merrill et al. (Merrill et al., 2015) were able to document that MM increases with decreasing personal UV dose. A multicenter case-control study conducted by Krone et al. (Krone et al., 2005) demonstrated a reduced risk of MM due to Bacille Calmette-Guerin (BCG) vaccination. The medical literature highlights that

transplant recipients developed *malignant melanoma via transmission* from the organ donors (Zwald et al., 2010). Furthermore, malignant melanoma can occur anywhere on the skin and even at *locations which are not exposed extensively to ultraviolet (UV) radiation* (Rohwedder et al., 2002; Yuan et al., 2017). In particular, the geographic distribution of age-standardised incidence rates of malignant cutaneous melanoma at latitudes closer to the equator are comparable to those incidence rates at latitudes > 55° (Stang et al., 2018; Ward and Jeffrey, 2017). Regardless of geographic latitude, the cumulative UV radiation dose of young adults is low. Still, malignant melanoma is among the most commonly diagnosed cancers in young adults worldwide (Schindler et al., 2014; Zhang et al., 2014). Strictly speaking, these and similar studies pose fundamental implications on the claimed relationship between UV radiation and malignant melanoma. In general, it is more than justified to consider the possibility that other risk factors like low cutaneous vitamin D 3 levels (Paolino et al., 2017), human endogenous retrovirus (Hahn et al., 2008; Cegolon et al., 2013; Gonzalez-Cao et al., 2016), human papilloma virus (Takamiyagi et al., 1998; Dréau et al., 2000; Biliris et al., 2000; La Placa et al., 2005; Roussaki-Schulze et al., 2005; Ambretti et al., 2007; Ruer et al, 2009) are primarily involved in the etiology of MM and not cumulative UV radiation dose. The primary treatment of melanoma is a surgical excision, sometimes radiotherapy is indicated. Under some specific circumstances a chemotherapy (Decarbazine, Temozolomide, Paclitaxel, Cisplatin, Carboplatin) or an immunotherapy including Interferon (IFN)-Alpha or anti-CTLA-4 anti-body ipilimumab or the use of BRAF/MEK inhibitors (vemurafenib, dabrafenib, trametinib) is offered to patients. The PD-1 antibodies pembrolizumab and nivolumab are approved for therapy of unresectable metastatic melanoma. Melanoma is able to metastasis to the brain with the consequence that patients with brain metastases have a life expectancy of only 3 to 5 months. One of the main causes of death in melanoma patients is widespread metastases. Even if new melanoma therapies are being developed rapidly, a cure of this many times deadly disease is still not in sight. To date evidence from epidemiologic studies and clinical observations on the relationship between increased exposure to ultraviolet (UV) radiation and the development of melanoma are inconclusive. Additional (Volgareva et al., 2016) research in the pathogenesis of melanoma is required.

2. Material and Methods

Most importantly and contrary to actual popular belief, no significant evidence exists between MM and personal UVB dose of any age or any skin type anywhere in the world (Godar et al., 2017).

2.0 Search Strategy

For the questions addressed in this paper, PubMed was searched for appropriate studies conducted in any country which investigated the relationship between malignant melanoma and several risk factors. The search in PubMed was performed while using medical key words like “Malignant melanoma” and “human papilloma virus” and “pcr” and “review” et cetera. The articles found where saved as a *.txt file while using PubMed support (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click bottom “create file”). The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles were considered for a review which provided access to data without any data access barrier; no data access restrictions were accepted. Additionally, references from relevant publications and review articles were checked. Furthermore, studies were excluded if data were self-contradictory or insufficient to calculate the measures of relationship.

2.1 The Data of the Studies Analyzed

The data of the studies reviewed are presented by several tables (**Table 1, Table 2, Table 3**). Takamiyagi et al. (Takamiyagi et al, 1998) detected HPV type 16 DNA was in the melanoma specimen in a case of a 37-year-old woman with malignant melanoma. Dréau et al. (Dréau et al., 2000) found the presence of HPV in 58% of the biopsy specimens obtained from patients with stage III and IV melanoma. Due to the missing control group, the data were not considered for a meta-analysis.

Ambretti et al. (Ambretti et al., 2007) developed a very sensitive method which combines an enzyme-amplified fluorescent in situ hybridization (ISH) for the detection of HPV nucleic acids (types 16 and 18) with a chemiluminescent immunohistochemistry (IHC) method for the detection of HPV genotypes in primary melanoma and found HPV nucleic acids in the range 60-80% of and malignant melanoma.

Table 1. The data of the studies considered for a meta-analysis

Study	Risk factor	Sample	Case	Case	Contol	Control	X^2 Value	X^2 Value	X^2 Value	X^2 Value	k	p value	Contra-
	i. e. Condition/Cause	size N	Pos.	Total	Pos.	Total	IMP	SINE	IMP*SINE	EXCL		(k)	diction = 1
Hahn et al. (Hahn et al., 2008)	Human endogenous retrovirus K antibodies	382	51	312	0	70	0,00	217,50	217,51	50,00	0,1859	0,000279155	0
Le Marchand et al. (Le Marchand et al., 2006)	Family history of malignant melanoma	556	21	278	4	278	0,49	236,66	237,15	16,81	0,1475	0,000503069	0
La Placa et al. (La Placa et al., 2005)	HPV GP-PCR DNA	71	14	51	0	20	0,02	26,12	26,14	13,02	0,3104	0,008920547	0
La Placa et al. (La Placa et al., 2005)	HPV GP-PCR DNA ISH	53	8	33	0	20	0,03	18,19	18,22	7,03	0,3282	0,016864334	0
Dréau et al. (Dréau et al., 2000)	HPV DNA		7	12									
Takamiyagi et al, 1998 (Takamiyagi et al, 1998)	HPV 16 ISH DNA		5	10									

Several studies investigated the relationship between malignant melanoma and risk factors like number of severe sunburns $\geq$ 9, total weekday sun exposure (hour) 1.751-4.650 (AMFS), total weekday sun exposure (hour) < 1.751 (AMFS), total weekday sun exposure (hour) > 8.46 (AMFS), hours worked outdoors over lifetime > 3361, number of sunbed uses per year $\geq$ 20, total number of sunbed uses > 250, regular exposure to sunbeds, burns from sun 3-5, severe burn and blistering and provided data which were not (**Table 2**) self-contradictory.

Table 2. The following studies failed to provide a significant relationship

Study	Risk factor	Sample	Case	Case	Contol	Control	X^2 Value	X^2 Value	X^2 Value	X^2 Value	k	p value	Contra-
	i. e. Condition/Cause	size N	Pos.	Total	Pos.	Total	IMP	SINE	IMP*SINE	EXCL		(k)	diction = 1
Green et al. (Green et al., 1985)	Number of severe sunburns >= 9	366	24	183	13	183	4,22	137,28	141,50	14,93	0,0997	0,056472993	0
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) 1,751–4,650 (AMFS)	1060	174	588	118	472	47,28	290,79	338,07	103,09	0,0511	0,096285803	0
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) < 1,751 (AMFS)	1060	172	588	118	472	47,61	293,61	341,21	101,42	0,0474	0,122774758	0
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) > 8,46 (AMFS)	1060	126	588	118	472	56,58	362,21	418,80	64,55	-0,0422	0,169807355	0
Le Marchand et al. (Le Marchand et al., 2006)	Hours worked outdoors over lifetime > 3361	556	64	278	51	278	22,18	163,96	186,14	35,06	0,0577	0,17345981	0
Westerdahl et al. (Westerdahl et al., 2000)	Number of sunbed uses per year >= 20	1484	44	571	55	913	30,00	485,47	515,47	19,11	0,0328	0,206517404	0
Westerdahl et al. (Westerdahl et al., 2000)	Total number of sunbed uses > 250	1484	31	571	37	913	19,59	509,74	529,33	13,68	0,0320	0,217261463	0
Westerdahl et al. (Westerdahl et al., 2000)	Regular exposure to sunbeds	1484	250	571	372	913	221,88	179,90	401,78	100,08	0,0300	0,248490133	0
Vogel et al. (Vogel et al., 2014)	Burns from sun 3-5	1852	172	906	188	946	97,66	593,84	691,50	81,70	-0,0112	0,629052329	0
Le Marchand et al. (Le Marchand et al., 2006)	Severe burn and blistering	556	19	278	18	278	8,28	240,37	248,64	9,25	0,0072	0,864885732	0

2.2 The following data are self-contradictory

In particular, a systemic and substantial under-detection of risk factors investigated and underestimation of its effect on malignant melanoma is at the end not excluded. Especially the data as presented by **Table 3** are self-contradictory and were not considered for a review.

Roussaki-Schulze et al. (Roussaki-Schulze et al., 2005) investigated the relationship between HPV and MM and were able to provide significant evidence that HPV is a sufficient condition of MM. The same study claims that HPV and MM are independent of each other. This is a contradiction. It appears to be that the control group was noct proerly used. Still, the data cannot be considered for further analysis. There are several contradictory studies investigating the involvement of HPV in melanoma, one of those is the study of Ruer et al. (Ruer et al., 2009). Ruer et al. (Ruer et al., 2009) conducted a controlled study to evaluate the relationship between HPV and melanoma and were able to provide evidence that without HPV no malignant melanoma. The causal relationship was greater than zero but still, the data of the same study demand that HPV and MM are independent of each other. This is a contradiction. Ruer et al. (Ruer et al., 2009) used a complementary wide excision (of healthy (?) skin) as an inappropriate internal control and failed to detect the true relationship between HPV and MM. Flight crews are exposed to several occupation-specific and potentially carcinogenic risk factors especially cosmic radiation. The study of dos Santos Silva et al. (dos Santos Silva et al., 2013)

Table 3. The following data of several studies are self-contradictory and were not considered for a meta-analysis

Study	Risk factor	Sample	Case	Case	Contol	Control	X^2	X^2	X^2 Value	X^2	k	p value	Contra-
							Value	Value		Value			
	i. e. Condition/Cause	size N	Pos.	Total	Pos.	Total	IMP	SINE	IMP^SINE	EXCL		(k)	diction = 1
Roussaki-Schulze et al. (Roussaki-Schulze et al., 2005)	HPV DNA	48	5	28	0	20	**0,05**	18,08	18,13	4,05	0,1922	**0,262379653**	1
dos Santos Silva et al., 2013 (dos Santos Silva et al., 2013)	Cumulative flight hours >= 5500	16329	43	66	5461	16263	**5417,34**	**7,67**	**5425,01**	**0,33**	**0,0424**	**6,12646E-08**	1
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) > 23,610 (GEM)	3260	321	1079	490	2181	**295,45**	**531,79**	**827,24**	**126,66**	**0,0793**	**5,99955E-06**	1
Martin-Gorgojo et al. (Martin-Gorgojo et al., 2017)	Burns from sun > 5	1852	560	906	492	946	**229,63**	**131,76**	**361,39**	**297,57**	**0,0989**	**2,07416E-05**	1
Godar et al. (Godar et al., 2016)	Burns from sun > 5	1852	560	906	492	946	**229,63**	**131,76**	**361,39**	**297,57**	**0,0989**	**2,07416E-05**	1
Vogel et al. (Vogel et al., 2014)	Burns from sun > 5	1852	560	906	492	946	**229,63**	**131,76**	**361,39**	**297,57**	**0,0989**	**2,07416E-05**	1
Osterlind (Osterlind, 1990)	Number of sunburns before age 15 > 5	1400	44	474	35	926	**15,07**	**389,18**	**404,24**	**23,95**	**0,1129**	**2,41359E-05**	1
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) 4,741–11,310 (GEM)	3260	218	1079	584	2181	**424,53**	**686,25**	**1110,78**	**58,99**	**-0,0718**	**4,1253E-05**	1
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) < 4,741 (GEM)	3260	226	1079	592	2181	**427,72**	**673,55**	**1101,26**	**62,16**	**-0,0673**	**0,000122452**	1
Vogel et al. (Vogel et al., 2014)	Burns from sun 0	1852	32	906	67	946	**44,67**	**842,17**	**886,84**	**10,02**	**-0,0789**	**0,000685024**	1
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) 11,311–23,610 (GEM)	3260	314	1079	515	2181	**319,31**	**541,67**	**860,98**	**118,56**	**0,0593**	**0,000709101**	1
Vogel et al. (Vogel et al., 2014)	Burns from sun 1-2	1852	142	906	199	946	**115,55**	**643,41**	**758,96**	**58,72**	**-0,0692**	**0,002915954**	1
Osterlind (Osterlind, 1990)	Number of sunburns during ages 15-24 > 5	1400	59	474	73	926	**39,82**	**362,47**	**402,29**	**25,93**	**0,0739**	**0,005686512**	1
Osterlind (Osterlind, 1990)	Number of sunburns in last 10 years >5	1400	24	474	24	926	**11,51**	**426,27**	**437,77**	**11,51**	**0,0643**	**0,016173695**	1
Le Marchand et al. (Le Marchand et al., 2006)	Drinking status: never	556	55	278	78	278	45,16	178,08	223,24	**22,33**	**-0,0970**	**0,022225633**	1
Vuong et al. (Vuong et al., 2013)	Total weekday sun exposure (hr) 4,651–8,460 (AMFS)	1060	116	588	118	472	59,00	378,08	437,08	**57,01**	**-0,0632**	**0,039702302**	1
Ruer et al. (Ruer et al., 2009)	HPV DNA	151	80	85	59	66	24,62	**0,24**	24,86	45,47	**0,0866**	**0,287092013**	1
Westerdahl et al. (Westerdahl et al., 2000)	Summer exposure to sunbed use	1484	4	571	9	913	5,56	562,04	567,59	**0,94**	**-0,0149**	**0,566160445**	1

Flight crews are exposed to several occupation-specific and potentially carcinogenic risk factors especially cosmic radiation. Dos Santos Silva et al. (dos Santos Silva et al., 2013) provided data which are self-contradictory. For the first, the causal relationship between cumulative flight hours of 5500 and more and malignant melanoma is highly significant and positive. The same study claims that cumulative flight hour of 5500 and more and malignant melanoma are excluding each other. This is a contradiction. If cumulative flight hours of 5500 and more and malignant melanoma are significantly excluding each other than the causal relationship k cannot be greater than zero. If it is true that the causal relationship between cumulative flight hours of 5500 and more and malignant melanoma is highly significant and positive then the conditio sine qua non relationship, or the conditio per quam relationship or both must be significant, which is not. The data are self-contradictory and cannot be considered for a review.

2.3 Statistical Analysis

All statistical analyses were performed with Microsoft Excel ® version 14.0.7166.5000 (32-Bit) software (Microsoft GmbH, Munich, Germany). All P values are two-sided; significance was indicated by a P value of less than 0.05. The following statistical tools and techniques were used to analyze the data.

2.3.1 The 2x2 Table

The 2x2 table in this article is defined (Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017), (Barukčić, 1989; Barukčić, 1997) in general more precisely (**Table 4**) as follows.

Table 4. **The sample space of a contingency table**

		Conditioned B_t		
		Yes = +1	*Not = +0*	*Total*
Condition A_t	Yes =+1	$\mathbf{a_t}$	$\mathbf{b_t}$	A_t
	Not = +0	$\mathbf{c_t}$	$\mathbf{d_t}$	$\underline{\mathbf{A_t}}$
	Total	B_t	$\underline{B_t}$	N_t

In general it is $(a+b) = A_t$, $(c+d) = \underline{A_t}$, $(a+c) = B_t$, $(b+d) = \underline{B_t}$ and $a_t+b_t+c_t+d_t=N_t$. Equally, it is $B_t+\underline{B_t} = A_t + \underline{A_t} = N_t$. In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or in other words $p(A_t)= p(A_t \cap B_t)+p(A_t \cap \underline{B_t})$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it should be considered that $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally that $p(\underline{B_t}) = 1- p(B_t) =p(b_t)+p(d_t)$. In point of fact, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. It is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$. These relationships are viewed by the table (**Table 5**) as follows.

Table 5. The probabilities of a contingency table

		Conditioned (i.e. Outcome) B_t		
		Yes = +1	*No = +0*	*Total*
Condition A_t	Yes =+1	$\mathbf{p(a_t) = p(A_t \cap B_t)}$	$\mathbf{p(b_t)}$	$\mathbf{p(A_t)}$
	No = +0	$\mathbf{p(c_t)}$	$\mathbf{p(d_t)}$	$\mathbf{p(\underline{A_t})}$
	Total	$\boldsymbol{p(B_t)}$	$\boldsymbol{p(\underline{B_t})}$	*1*

2.3.2 Independence

Data as such can be continuous, ordinal, or categorical. Still, in the case of independence of A_t and B_t it is

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \times p\left(B_t\right) \tag{1}$$

2.3.3 Exclusion (A_t excludes B_t and vice versa relationship)

The mathematical formula of the exclusion relationship (A_t excludes B_t and vice versa) of a population was defined as

$$p(A_t \mid B_t) \equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p(a_t) \equiv p(b_t) + p(c_t) + p(d_t) \equiv p(c_t) + (1 - p(B_t)) \equiv p(b_t) + (1 - p(A_t)) \equiv +1 \quad (2)$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

2.3.4 Sufficient Condition (Conditio Per Quam; Material Conditional)

A given disease (i.e. effect) can be caused by only one causal mechanism but this must not be the case. A causal relationship can be described in terms of sufficient conditions/causes too and points to the possibility of multicausality. The mathematical formula of the sufficient condition relationship (conditio per quam) (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; Barukčić, 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić, 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c; Barukčić, 2018a; Barukčić, 2018b; Barukčić, 2018c) of a population was defined as

$$p(A_t \rightarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{A}_t) \equiv p(A_t \cap B_t) + (1 - p(A_t)) \equiv p(a_t) + p(c_t) + p(d_t) \equiv p(d_t) + p(B_t) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv +1 \quad (3)$$

and used to proof the hypothesis: *if* A_t *then* B_t .

2.3.5 Necessary Condition (Conditio Sine Qua Non)

Causation is an essential concept in human medicine and corresponds not only with major approaches to causation found in the philosophical literature but has consequences which reach far beyond medicine itself. A necessary event is an event (i. e. condition/cause) without which another event (i.e. conditioned/effect) cannot occur. The formula of the necessary condition (conditio sine qua non) relationship (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; Barukčić, 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić, 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c; Barukčić, 2018a; Barukčić, 2018b; Barukčić, 2018c) was derived as

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{B}_t) \equiv p(A_t \cap B_t) + (1 - p(B_t)) \equiv p(a_t) + p(b_t) + p(d_t) \equiv \frac{a_t + b_t + d_t}{N} \equiv +1 \quad (4)$$

and used to proof the hypothesis: *without* A_t *no* B_t.

2.3.6 Necessary and Sufficient Condition (Material Biconditional)

The *necessary and sufficient condition* relationship (Barukčić, 1989; Barukčić, 1997; Barukčić, 2005; Barukčić, 2006a; Barukčić, 2006b; Barukčić, 2011a; Barukčić, 2011b; Barukčić, 2012; Barukčić, 2016a; Barukčić, 2016b; Barukčić, 2016c; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c; Barukčić, 2018a; Barukčić, 2018b; Barukčić, 2018c) was defined as

$$p(A_t \leftrightarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{A}_t \cap \underline{B}_t) \equiv \frac{a_t + d_t}{N} \equiv +1 \quad (5)$$

2.4 The data of a study are self-contradictory

The conclusions of studies concerned with causality are potentially endangered by the quality of the data, by nonrandom systematic error in the design or conduct of a study (bias), by confounding, by measurement errors, by an inappropriate design of a study and incorrect 'cut off'-values of measured factors, by the statistics used and

other factors too. Regardless of terminology, especially the bias caused by different confounders may result in an underestimation or an overestimation of the exposure effect. In practice, one way to address confounding is to identify and control confounders, randomization, blinding and matching (Kocher & Zurakowski, 2004) can decrease confounding. In point of fact, empirical or study data as such must meet some formal theoretical and mathematical requirements to be of use to prove causality from data alone. Otherwise and for preliminary purposes the same data must be regarded as self-contradictory and must be treated as inappropriate for causal analysis or labelled as potentially and significantly determined by known or unknown confounders. The standard to prove cause-effect relationships is set higher than the standard to suggest only an association. Strictly speaking, it is very unlikely to establish a significant causal relationship from data which are self-contradictory.

2.4.1 The X^2 Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square (Pearson, 1900) goodness of fit test cannot be used it is possible to use an approximate and conservative (one sided) confidence interval as discussed by Rumke (Rumke, 1975), Louis (Louis, 1981), Hanley et al. (Hanley & Lippman-Hand, 1983) and Jovanovic (Jovanovic & Levy, 1997) known as the rule of three. According to the definition of the conditio sine qua non relationship it is

$$p(A_t \cap B_t) + (1 - p(B_t)) \equiv +1 \tag{6}$$

or

$$p(A_t \cap B_t) + 1 - p(B_t) \equiv +1 \tag{7}$$

or

$$p(A_t \cap B_t) - p(B_t) \equiv 0 \tag{8}$$

or

$$p(A_t \cap B_t) \equiv p(B_t) \tag{9}$$

Multiplying equation before by the population or sample size N, it is

$$N \times p(A_t \cap B_t) \equiv N \times p(B_t) \tag{10}$$

or

$$N \times p(A_t \cap B_t) - N \times p(B_t) = 0 \tag{11}$$

The square operation yields

$$(N \times p(A_t \cap B_t) - N \times p(B_t)) \times (N \times p(A_t \cap B_t) - N \times p(B_t)) = 0 \times 0 \tag{12}$$

Dividing by $N \times p(B_t)$ we obtain

$$\frac{(N \times p(A_t \cap B_t) - N \times p(B_t))^2}{N \times p(B_t)} = 0 \tag{13()}$$

which is equivalent with

$$\frac{(a_t - (B_t))^2}{(B_t)} = \frac{(a_t - (a_t + c_t))^2}{(B_t)} = \frac{(c_t)^2}{(B_t)} = 0 \tag{14}$$

Adding $\mathbf{(((b_t+d_t)-(b_t+d_t))^2/(b_t+d_t)) = 0}$ yields

$$\frac{(c_t)^2}{(B_t)} + 0 = 0 + 0 = 0 \tag{15}$$

Using Yates continuity correction (Yates, 1934), the chi-square value of a conditio sine qua non distribution follows as

$$\chi^2(A_t \leftarrow B_t) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{(B_t)} + 0 = 0 \tag{16}$$

This definition of the X^2 distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published (Barukčić, 2018; Barukčić, 2018; Barukčić, 2018) formulas and can be used to prove whether the data of a study do support a conditio-sine qua non Null-hypothesis: *without* A_t *no* B_t. Even if the data support such a null-hypothesis, the question is justified, can we rely on the result? In other words, it is necessary to search for contradictions with the data itself. From the definition of the conditio sine qua non above it is

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + (1 - p(B_t)) \equiv +1 \tag{17}$$

or at the end

$$p(A_t \cap B_t) = p(B_t) \tag{18}$$

There are circumstances, where the two factors A_t and B_t investigated are independent of each other. In other words, the causal relationship between A_t and B_t is equal to $\mathbf{k(A_t, B_t) = 0}$ or it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{19}$$

If a conditio sine qua non is given, it is equally $\mathbf{p(A_t, B_t) = p(B_t)}$.Rearranging equation before, we obtain

$$p(B_t) \equiv p(A_t) \times p(B_t) \tag{20}$$

and at the end after division by $p(B_t)$

$$1 \equiv p(A_t) \tag{21}$$

In other words, due to formal mathematical requirements, the data of a study must be treated as self-contradictory if the data of the same study do support a significant conditio sine qua non relationship between the two factors A_t and B_t while at the same time the same data do support the hypothesis too, that the two factors A_t and B_t are independent of each other. Such data are inappropriate to establish a cause effect relationship.

Under conditions where the causal relationship between the two factors A_t and B_t $k(A_t, B_t) < 0$ while there is a significant conditio sine qua non relationship between the two factors A_t and B_t investigated, the data must be treated as self-contradictory too and cannot be used for causal analysis. If the causal relationship is $\mathbf{k(A_t, B_t) < 0}$, then it is

$$p(A_t \cap B_t) < p(A_t) \times p(B_t) \tag{22}$$

If a significant conditio sine qua non relationship is given, then it is $\mathbf{p(A_t, B_t) = p(B_t)}$. Rearranging equation above, we obtain

$$p(B_t) < p(A_t) \times p(B_t) \tag{23}$$

or at the end

$$1 < p(A_t) \tag{24}$$

Still, *there is no probability which is greater than 1*. In other words, data which support a negative causal relationship and equally a conditio sine qua non relationship are self-contradictory (**Table 6**) and inappropriate for causal analysis.

Table 6. Conditio sine qua non in more detail.

		Signifiant *conditio sine qua non* relationship	
		Yes	No
causal	k > 0	Ok	Ok (IMP?)
relationship	k = 0	**Contradiction!**	Ok (no relationship)
	k < 0	**Contradiction!**	Ok (EXCL?)

2.4.2 The X^2 Goodness of Fit Test of a sufficient condition (conditio per quam)

Pearson's chi-square (Pearson, 1900) goodness of fit test cannot be used under any (Barnard, 1947; Gorroochurn, 2016) circumstances. Under what possible circumstances is it the case that Pearson's chi-square goodness of fit test is of use can be found in literature (Yamane, 1964). The rule of three discussed by Rumke (Rumke, 1975), Louis (Louis, 1981), Hanley et al. (Hanley & Lippman-Hand, 1983) and Jovanovic (Jovanovic & Levy, 1997) is an approximate and conservative (one sided) confidence interval and of use in this context too. According to the definition of the conditio per quam relationship it is

$$p(A_t \cap B_t) + (1 - p(A_t)) \equiv +1 \tag{25}$$

or

$$p(A_t \cap B_t) + 1 - p(A_t) \equiv +1 \tag{26}$$

or

$$p(A_t \cap B_t) - p(A_t) \equiv 0 \tag{27}$$

or

$$p(A_t \cap B_t) \equiv p(A_t) \tag{28}$$

Multiplying equation before by the population or sample size N, it is

$$N \times p(A_t \cap B_t) \equiv N \times p(A_t) \tag{29}$$

or

$$N \times p(A_t \cap B_t) - N \times p(A_t) = 0 \tag{30}$$

The square operation yields

$$\left(N\times p\left(A_t\cap B_t\right)-N\times p\left(A_t\right)\right)\times\left(N\times p\left(A_t\cap B_t\right)-N\times p\left(A_t\right)\right)=0\times 0 \tag{31}$$

Dividing by $N\times p(B_t)$ we obtain

$$\frac{\left(N\times p\left(A_t\cap B_t\right)-N\times p\left(A_t\right)\right)^2}{N\times p\left(A_t\right)}=0 \tag{32}$$

which is equivalent with

$$\frac{\left(a_t-\left(A_t\right)\right)^2}{\left(A_t\right)}=\frac{\left(a_t-\left(a_t+b_t\right)\right)^2}{\left(A_t\right)}=\frac{\left(b_t\right)^2}{\left(A_t\right)}=0 \tag{33}$$

Adding $(((c_t+d_t)-(c_t+d_t))^2/(c_t+d_t)) = 0$ yields

$$\frac{\left(a_t\right)^2}{\left(A_t\right)}+0=0+0=0 \tag{34}$$

Using Yates continuity correction (Yates, 1934), the chi-square value of a conditio sine qua non distribution follows as

$$\chi^2\left(A_t\rightarrow B_t\right)\equiv\frac{\left(a_t-\left(\frac{1}{2}\right)\right)^2}{\left(A_t\right)}+0=0 \tag{35}$$

This definition of the X^2 distribution of a *conditio per quam* (Barukčić, 2018; Barukčić, 2018; Barukčić, 2018) distribution (degrees of freedom d.f. = 2-1=1) can be used to prove whether the data of a study do support a conditio per quam Null-hypothesis: *if* A_t *then* B_t. Even if the data of as certain study support such a null-hypothesis, the question is justified, can we rely on the data of the study and such a result? In other words, it is necessary to search for contradictions within the data of the study itself. From the definition of the conditio per quam relationship above it is

$$p\left(A_t\rightarrow B_t\right)\equiv p\left(A_t\cap B_t\right)+\left(1-p\left(A_t\right)\right)\equiv+1 \tag{36}$$

or at the end

$$p\left(A_t\cap B_t\right)=p\left(A_t\right) \tag{36}$$

There are circumstances, where the two factors A_t and B_t investigated are independent of each other. In other words, the causal relationship between A_t and B_t is equal to $\mathbf{k(A_t, B_t)=0}$ or it is

$$p\left(A_t\cap B_t\right)\equiv p\left(A_t\right)\times p\left(B_t\right) \tag{37}$$

Under circumstances of a conditio per quam relationship it is $\mathbf{p(A_t, B_t) = p(A_t)}$ and we obtain

$$p\left(A_t\right)\equiv p\left(A_t\right)\times p\left(B_t\right) \tag{38}$$

or at the end

$$1\equiv p\left(B_t\right) \tag{39}$$

In other words, due to formal aspects, the data of a study must be treated as self-contradictory if the data of the same study do support a significant *conditio per quam* relationship between the two factors A_t and B_t while the same data do support the hypothesis too, that the two factors A_t and B_t are independent of each other. Such data are inappropriate to establish a cause effect relationship. Under conditions where the causal relationship between the two factors A_t and B_t is $\mathbf{k(A_t, B_t) < 0}$ while there is a significant conditio per quam relationship between the two factors A_t and B_t investigated, the data must be treated as self-contradictory too and cannot be used for causal analysis. If the causal relationship is $k(A_t, B_t) < 0$, then it is

$$p(A_t \cap B_t) < p(A_t) \times p(B_t) \tag{40}$$

If a significant conditio per quam relationship is given, then it is $\mathbf{p(A_t, B_t) = p(A_t)}$. Rearranging equation above, we obtain

$$p(A_t) < p(A_t) \times p(B_t) \tag{41}$$

or at the end

$$1 < p(B_t) \tag{42}$$

Again, *there is no probability which is greater than 1*. In other words, data which support a negative causal relationship and equally a conditio per quam relationship are self-contradictory and inappropriate for causal analysis.

Table 7. Conditio per quam in more detail.

		Signifiant *conditio per quam* relationship	
		Yes	No
causal relationship	k > 0	Ok	Ok (SINE?)
	k = 0	**Contradiction!**	Ok (no relationship)
	k < 0	**Contradiction!**	Ok (EXCL?)

2.4.3 The X^2 Goodness of Fit Test of the exclusion relationship (Exclusio)

The justification of inferences or procedures which extrapolate from sample data to the population or general facts is a central problem of statistics itself. The problem of induction is not addressed, nor is the article concerned with details to justify the correctness of statistical methods. Despite disagreements, it is insightful to recall that the relation between data and hypotheses is of use to determine how believable a hypothesis is and a way to avoid invalid inference. But, as can be imagined, insufficient statistical methods (i.e. risk ratio) used to analyze data but confounding too has influence on a valid inference especially in studies concerned with causality and it is hard to avoid incorrect conclusions in principle. A good study design has the potential for reducing confounding but does not guarantee valid inference. Still, hypotheses can be evaluated in the light of empirical facts while using some specific statistical methods. The chi square is such a statistical method which can be used for discrete distributions like the binomial distribution and the Poisson distribution but requires a sufficient sample size (n >30) in order to be valid. The *chi-square Goodness of fit test* compares how well an *empirical distribution* fits a theoretical distribution. The Null hypothesis of Chi-Square goodness of fit test (Yamane, 1964) assumes that there is no significant difference between an empirical distribution and a theoretical distribution. In contrast to this, the chi-square test for independence compares two sets of data. For continuous distributions, the Kolmogorov-Smirnov (Sachs, 1992) and Anderson-Darling goodness of fit tests (Sachs, 1992) are used. Under conditions where the

chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et al. 1983; Louis, 1981; Jovanovic et al., 1997). According to the definition of the *exclusion relationship* it is and has to be that

$$p(b_t)+p(c_t)+p(d_t)\equiv+1 \tag{43}$$

Rearranging this equation, we obtain

$$p(b_t)=1-p(c_t)-p(d_t)=1-\left(p(c_t)+p(d_t)\right)\equiv 1-p(\underline{A}_t)=p(A_t) \tag{44}$$

and

$$p(c_t)=1-p(b_t)-p(d_t)\equiv 1-\left(p(b_t)+p(d_t)\right)=1-p(\underline{B}_t)=p(B_t) \tag{45}$$

The chi square goodness of fit test of the exclusion relationship can be derived as follows.

$$\begin{aligned} N\times p(b_t) &= N\times p(A_t) \\ \left(N\times p(b_t)-N\times p(A_t)\right) &= 0 \\ \left(N\times p(b_t)-N\times p(A_t)\right)\times\left(N\times p(b_t)-N\times p(A_t)\right) &= 0\times 0 \end{aligned}$$

$$\frac{\left(N\times p(b_t)-N\times p(A_t)\right)^2}{N\times p(A_t)} = \frac{0}{N\times p(A_t)}=0 \tag{46}$$

$$\chi^2(b_t)=\frac{\left(N\times p(b_t)-N\times p(A_t)\right)^2}{N\times p(A_t)}=\frac{\left(b_t-(a_t+b_t)\right)^2}{A_t}=\frac{\left(-(a_t)\right)^2}{A_t} = 0$$

$$\chi^2(b_t)=\frac{\left(-(a_t)-0,5\right)^2}{A_t} = 0$$

and as

$$\begin{aligned} N\times p(c_t) &= N\times p(B_t) \\ \left(N\times p(c_t)-N\times p(B_t)\right) &= 0 \\ \left(N\times p(c_t)-N\times p(B_t)\right)\times\left(N\times p(c_t)-N\times p(B_t)\right) &= 0\times 0 \end{aligned}$$

$$\frac{\left(N\times p(c_t)-N\times p(B_t)\right)^2}{N\times p(B_t)} = \frac{0}{N\times p(B_t)}=0 \tag{47}$$

$$\chi^2(b_t)=\frac{\left(N\times p(c_t)-N\times p(B_t)\right)^2}{N\times p(B_t)}=\frac{\left(c_t-(a_t+c_t)\right)^2}{B_t}=\frac{\left(-(a_t)\right)^2}{B_t} = 0$$

$$\chi^2(c_t)=\frac{\left(-(a_t)-0,5\right)^2}{B_t} = 0$$

The chi square value with degree of freedom d.f. = 2-1=1of the exclusion relationship with a continuity correction can be calculated as

$$\chi^2\left(\mathrm{EXCL}\right)=\frac{\left(-(a_t)-0,5\right)^2}{A_t}+\frac{\left(-(a_t)-0,5\right)^2}{B_t} \tag{48}$$

This definition of the X^2 distribution of a *exclusion* distribution (degrees of freedom d.f.= 2-1=1) is already discussed in literature (Barukčić, 2018; Barukčić, 2018; Barukčić, 2018). The null-hypothesis A_t *excludes* B_t *and vice versa* can be tested while using the chi square distribution. Even if the data of a study support the null-hypothesis A_t *excludes* B_t *and vice versa*, the question is justified, can we rely on such a result? In other words, are there any contradictions present within the data analyzed itself? From the definition of the A_t *excludes* B_t *and vice versa* relationship above it is

$$p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right)\equiv+1 \tag{49}$$

or at the end

$$p\left(b_t\right)=1-p\left(c_t\right)-p\left(d_t\right)=1-\left(p\left(c_t\right)+p\left(d_t\right)\right)\equiv1-p\left(\underline{A}_t\right)=p\left(A_t\right) \tag{50}$$

and

$$p\left(c_t\right)=1-p\left(b_t\right)-p\left(d_t\right)\equiv1-\left(p\left(b_t\right)+p\left(d_t\right)\right)=1-p\left(\underline{B}_t\right)=p\left(B_t\right) \tag{51}$$

There are circumstances, where the two factors A_t and B_t investigated are *independent* of each other. In other words, the causal relationship between A_t and B_t is equal to $\mathbf{k(A_t, B_t)=0}$ or it is

$$p\left(A_t\cap B_t\right)\equiv p\left(A_t\right)\times p\left(B_t\right) \tag{52}$$

Under conditions of an exclusion relationship it is $\mathbf{p(c_t) = p(B_t)}$ **and** $\mathbf{p(b_t) = p(A_t)}$**.** Thus far, rearranging the equation before, we obtain

$$p\left(A_t\cap B_t\right)\equiv p\left(b_t\right)\times p\left(c_t\right) \tag{53}$$

Under conditions of an exclusion relationship it is $\mathbf{p(A_t, B_t) = 0}$. Thus far, it is

$$0\equiv p\left(b_t\right)\times p\left(c_t\right) \tag{54}$$

In other words, under condition where the causal relationship between the two factors A_t and B_t is $k(A_t, B_t) = 0$ and were the same two factors A_t and B_t are equally excluding each other it equally true that $p(A_t, B_t) = 0$ and that $p(c_t)\times p(b_t) = 0$. Under these circumstances it is $p(B_t) = p(A_t, B_t) + p(c_t) = 0$ or $p(A_t) = p(A_t, B_t) + p(b_t) = 0$. Such data are inappropriate for causal analysis. Data which support the hypothesis that two factors A_t and B_t investigated are *independent* of each other and equally that the same two factors A_t and B_t investigated are *excluding* of each other are self-contradictory and inappropriate to establish a cause effect relationship. Furthermore, under conditions where the causal relationship between the two factors A_t and B_t is $\mathbf{k(A_t, B_t) > 0}$ while there is a significant exclusion relationship between the same two factors A_t and B_t investigated, the data must be treated as self-contradictory too and cannot be used for causal analysis. If the causal relationship is $k(A_t, B_t) > 0$, then it is

$$p(A_t \cap B_t) > p(A_t) \times p(B_t) \tag{55}$$

Under conditions of an exclusion relationship it is $\mathbf{p(A_t, B_t) = 0}$. Thus far, rearranging the equation before, we obtain

$$0 > p(A_t) \times p(B_t) \tag{56}$$

Under conditions where $k(A_t, B_t) > 0$ it is equally $\mathbf{p(A_t) > 0}$ **and** $\mathbf{p(B_t) > 0}$. Thus far, it is possible and allowed to divide by $p(A_t) \times p(B_t)$. Dividing by $p(A_t) \times p(B_t)$ we obtain

$$\frac{0}{p(A_t) \times p(B_t)} > \frac{p(A_t) \times p(B_t)}{p(A_t) \times p(B_t)} \tag{57}$$

In general, under these conditions we must accept

$$+0 > +1 \tag{58}$$

which is a logical contradiction. Thus far, data which forces us to accept that there is a causal relationship which is $k(A_t, B_t) > 0$ and that equally the same two factors A_t and B_t investigated are *excluding* of each other are self-contradictory and inappropriate for causal analysis. In other words, the mathematical formula of the causal relationship k (Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017), (Barukčić, 1989; Barukčić, 1997) is defined *at every single event t*, *at every single Bernoulli trial t*, as

$$k(A_t, B_t) \equiv \frac{\left(p(a_t) - \left(p(A_t) \times p(B_t)\right)\right)}{\sqrt[2]{\left(p(A_t) \times p(\underline{A}_t)\right) \times \left(p(B_t) \times p(\underline{B}_t)\right)}} \tag{59}$$

where A_t denotes the cause and B_t denotes the effect. Under conditions where there is a significant cause and effect relationship and equally a significant exclusion relationship it is $\mathbf{p(a_t) = p(A_t, B_t) = 0}$ and it follows that

$$k(A_t, B_t) \equiv \frac{\left(0 - \left(p(A_t) \times p(B_t)\right)\right)}{\sqrt[2]{\left(p(A_t) \times p(\underline{A}_t)\right) \times \left(p(B_t) \times p(\underline{B}_t)\right)}} < 0 \tag{60}$$

In other words, an exclusion relationship demands a causal relationship which is $k(A_t, B_t) < 0$ and vice versa. Otherwise there is evidence that the data used are self-contradictory and it is difficult to consider the same data for causal analysis.

Table 8. Exclusion relationship in more detail.

		Signifiant exclusion relationship	
		Yes	No
causal relationship	$k > 0$	**Contradiction!**	Ok (SINE? IMP?)
	$k = 0$	**Contradiction!**	Ok (no relationship?)
	$k < 0$	**Yes**	OK (A_t OR B_t?)

2.4.4 The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k (Barukčić, 2005; Barukčić, 2006; Barukčić, 2006; Barukčić, 2009; Barukčić, 2017), (Barukčić, 1989; Barukčić, 1997) is defined *at every single event t*, *at every single Bernoulli trial t*, as

$$k\left(A_t, B_t\right) \equiv \frac{\left(p\left(A_t \times B_t\right) - \left(p\left(A_t\right) \times p\left(B_t\right)\right)\right)}{\sqrt[2]{\left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)}} \tag{61}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution (Pearson K, 1900) can be applied to determine the significance (Barukčić, 2016) of causal relationship k. Correlation (Bravais, 1846; Pearson, 1896; Wright, 1921) is not causation, causation is not correlation. The relationship between correlation and causation (Wright, 1921) is discussed in many publications. This does not necessarily imply that repeating itself over and over again may contribute anything new to further scientific progress.

Under conditions where a random variable A_t is a cause of the random variable B_t and *only* a necessary condition too, the chi square value of the causal relationship can be simplified as follows.

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{N \times N \times \left(p\left(A_t \times B_t\right) - \left(p\left(A_t\right) \times p\left(B_t\right)\right)\right)^2}{N \times N \times \left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)} \tag{62}$$

where A_t denotes the cause and B_t denotes the effect. Under conditions where A_t is equally a necessary condition of B_t it is

$$p\left(A_t \cap B_t\right) \equiv p\left(B_t\right) \tag{63}$$

Substituting this relationship into equation before we obtain

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{N \times N \times \left(p\left(B_t\right) - \left(p\left(A_t\right) \times p\left(B_t\right)\right)\right)^2}{N \times N \times \left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)} \tag{64}$$

or the relationship

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{N \times N \times \left(p\left(B_t\right) \times \left(1 - p\left(A_t\right)\right)\right)^2}{N \times N \times \left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)} \tag{65}$$

or the relationship

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{N \times N \times p\left(B_t\right)^2 \times \left(1 - p\left(A_t\right)\right)^2}{N \times N \times \left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)} \tag{66}$$

Equation can be simplified as

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{N \times N \times p\left(B_t\right) \times \left(1 - p\left(A_t\right)\right)}{N \times N \times \left(p\left(A_t\right) \times\right) \times \left(\times p\left(\underline{B}_t\right)\right)} = \frac{N \times p\left(B_t\right) \times N \times \left(1 - p\left(A_t\right)\right)}{N \times p\left(A_t\right) \times N \times p\left(\underline{B}_t\right)} \tag{67}$$

or at the end as

$$\chi\left(k\right) \equiv N \times k\left(A_t, B_t\right)^2 \equiv N \times \frac{B_t \times \underline{A}_t}{A \times \underline{B}_t} = \frac{E\left(B_t\right) \times E\left(A_t\right)}{E\left(A_t\right) \times E\left(\underline{B}_t\right)} \tag{68}$$

Under conditions where a random variable A_t is a cause of the random variable B_t and *only* a sufficient condition too, it has to be that

$$p(A_t \cap B_t) \equiv p(A_t) \tag{69}$$

and the chi square value of the causal relationship can be derived as

$$\chi(k) \equiv N \times k(A_t, B_t)^2 \equiv N \times \frac{A_t \times \underline{B}_t}{B \times \underline{A}_t} = \frac{E(A_t) \times E(B_t)}{E(B_t) \times E(\underline{A}_t)} \tag{70}$$

Another simple form of a X^2 square goodness of fit test can be derived as follows. Under conditions of independence it is

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{71}$$

or

$$p(A_t \cap B_t) - p(A_t) \times p(B_t) = 0 \tag{72}$$

or

$$\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right) \times \left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right) = 0 \times 0 = 0 \tag{73}$$

or

$$\frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{74}$$

If the probability changes from trial ***t*** to trial *t*, we obtain

$$\chi^2 = \sum_{t=+1}^{N} \frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{75}$$

If the probability is constant form trial to trial it is

$$\chi^2 = N \times \frac{\left(p(A_t \cap B_t) - p(A_t) \times p(B_t)\right)^2}{p(A_t) \times p(B_t)} = 0 \tag{76}$$

2.3.6 The Chi Square Distribution

The chi-squared test as published by K. Pearson (Pearson, 1900) as was already derived (Bienaymé, 1852) in 1852 especially by the French statistician Irenée-Jules Bienaymé (1796–1878). A chi-square random variable is treated as the sum of squares of independently distributed standard normal random variables. The chi-square goodness-of-fit statistic compares the number of real observations to the number expected observations. Yates' correction (Yates, 1934) can applied when more than 1/5 of the expected values are smaller than five and when there are cells with zero count. While evaluating hypotheses in the light of empirical facts, the following critical values of the chi square distribution as visualized by **Table 9** can be considered.

Table 9. The critical values of the chi square distribution (degrees of freedom: 1)

	p-Value	One sided X^2	Two sided X^2
The chi square distribution	0.1000000000	1.642374415	2.705543454
	0.0500000000	**2.705543454**	**3.841458821**
	0.0400000000	3.06490172	4.217884588
	0.0300000000	3.537384596	4.709292247
	0.0200000000	4.217884588	5.411894431
	0.0100000000	5.411894431	6.634896601
	0.0010000000	9.549535706	10.82756617
	0.0001000000	13.83108362	15.13670523
	0.0000100000	18.18929348	19.51142096
	0.0000010000	22.59504266	23.92812698
	0.0000001000	27.03311129	28.37398736
	0.0000000100	31.49455797	32.84125335
	0.0000000010	35.97368894	37.32489311
	0.0000000001	40.46665791	41.82145620

3. Results

3.1 Several potential risk factors and malignant melanoma are independent of each other

Several studies provided self-contradictory data (**Table 3**) and were considered for further analysis. Besides of possible bias other studies could be re-analyzed (**Table 2**).

Claims.

Null hypothesis:

Risk factors like number of severe sunburns ≥ 9 (Green et al., 1985), total weekday sun exposure (hr) 1,751–4,650 (AMFS)(Vuong et al., 2013), total weekday sun exposure (hr) < 1,751 (AMFS) (Vuong et al., 2013), total weekday sun exposure (hr) > 8,46 (AMFS)(Vuong et al., 2013), hours worked outdoors over lifetime > 3361(Le Marchand et al., 2006), number of sunbed uses per year $\geq$ 20 (Westerdahl et al., 2000),total number of sunbed uses > 250 (Westerdahl et al., 2000), regular exposure to sunbeds (Westerdahl et al., 2000),burns from sun 3-5 (Vogel et al., 2014), severe burn and blistering (Le Marchand et al., 2006) and malignant melanoma are independent of each other. $k = 0$.

Alternative hypothesis:

Risk factors like number of severe sunburns ≥ 9 (Green et al., 1985), total weekday sun exposure (hr) 1,751–4,650 (AMFS)(Vuong et al., 2013), total weekday sun exposure (hr) < 1,751 (AMFS) (Vuong et al., 2013), total weekday sun exposure (hr) > 8,46 (AMFS)(Vuong et al., 2013), hours worked outdoors over lifetime > 3361(Le Marchand et al., 2006), number of sunbed uses per year $\geq$ 20 (Westerdahl et al., 2000),total number of sunbed uses > 250 (Westerdahl et al., 2000), regular exposure to sunbeds (Westerdahl et al., 2000), burns from sun 3-5 (Vogel et al., 2014), severe burn and blistering (Le Marchand et al., 2006) and malignant melanoma are not independent of each other. $k \neq 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

The relationship between the risk factors mentioned and malignant melanoma were investigated by several studies (**Table 2**). The data as presented by **Table 2** were not self-contradictory. Neither the number of severe sunburns ≥ 9 (Green et al., 1985), nor the total weekday sun exposure (hr) 1,751–4,650 (AMFS) (Vuong et al., 2013), nor the total weekday sun exposure (hr) < 1,751 (AMFS) (Vuong et al., 2013), nor the total weekday sun exposure (hr) > 8,46 (AMFS)(Vuong et al., 2013), nor the hours worked outdoors over lifetime > 3361 (Le Marchand et al., 2006), nor the number of sunbed uses per year $\geq$ 20 (Westerdahl et al., 2000), nor the total number of sunbed uses > 250 (Westerdahl et al., 2000), nor the regular exposure to sunbeds (Westerdahl et al., 2000), nor the burns from sun 3-5 (Vogel et al., 2014), nor the severe burn and blistering (Le Marchand et al., 2006) are causally related with

malignant melanoma. In the same respect, none of the studies mentioned were able to provide some evidence that there is a necessary condition relationship, or a sufficient condition relationship, or an exclusion relationship between the risk factors investigated and malignant melanoma. In other words, malignant melanoma is not determined by neither the number of severe sunburns ≥ 9 (Green et al., 1985), nor the total weekday sun exposure (hr) 1,751–4,650 (AMFS) (Vuong et al., 2013), nor the total weekday sun exposure (hr) < 1,751 (AMFS) (Vuong et al., 2013), nor the total weekday sun exposure (hr) > 8,46 (AMFS)(Vuong et al., 2013), nor the hours worked outdoors over lifetime > 3361 (Le Marchand et al., 2006), nor the number of sunbed uses per year ≥ 20 (Westerdahl et al., 2000), nor the total number of sunbed uses > 250 (Westerdahl et al., 2000), nor the regular exposure to sunbeds (Westerdahl et al., 2000), nor the burns from sun 3-5 (Vogel et al., 2014), nor the severe burn and blistering (Le Marchand et al., 2006). **Q. e. d.**

3.2 The Study of Le Marchand et al. (Le Marchand et al., 2006)

The uncertainty about sunlight exposure and the risk of cutaneous melanoma is no longer justified (**Table 2, Table 3**). Westerdahl et al. found that an excessive use of sunscreens was not found to protect against malignant melanoma (Westerdahl et al., 1995). Furthermore, an excessive use of sunscreens was not able successfully to prevent from an in the incidence of MM (Vainio et al., 2000). Other factors than sunlight exposure are responsible for malignant melanoma.

Claims.

Null hypothesis:

A family history of malignant melanoma and malignant melanoma are not causally related, both are independent of each other. $k = 0$.

Alternative hypothesis:

A family history of malignant melanoma and malignant melanoma are causally related, both are not independent of each other. $k \neq 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

Le Marchand et al. (Le Marchand et al., 2006) conducted a population-based case-control study and investigated the relationship between family history of malignant melanoma and malignant melanoma. The data are illustrated by **Table 10**.

Table 10. The data of Le Marchand et al. (Le Marchand et al., 2006)

		Malignant melanoma B_t		
		Yes = +1	*No = +0*	*Total*
Family history of malignant melanoma A_t	Yes =+1	21	**4**	25
	No = +0	257	274	531
	Total	278	278	556

The study of Le Marchand et al. (Le Marchand et al., 2006) provided highly significant evidence that a family history of malignant melanoma is causally related to malignant melanoma (p (IMP)=0.992805755, X^2 (IMP)=0.49, k=0.147547432, p value (k)=0.000503069) itself. **Q. e. d.**

3.3 The Study of La Placa et al. (La Placa et al., 2005)

Over hundred eighteen papillomavirus (PV) types have been completely sequenced (de Villiers et al., 2004). In general, it is known that different HPVs may infect mucosal epithelium or human skin (Jablonska and Majewski, 1994). Human papillomaviruses (HPVs) are frequently (Hazard et al., 2007; Hsu et al., 2009) found in healthy skin. In fact, it comes as no surprise that HPV was found even in malignant melanoma specimens. Takamiyagi et al, 1998 (Takamiyagi et al, 1998) detected HPV type 16 DNA in the melanoma specimen by polymerase chain reaction (PCR) and in situ hybridization (ISH). According to Dréau et al. (Dréau et al., 2000) seven of 12 (58%) melanoma biopsy specimens were positive for HPV by immunohistochemistry. Roussaki-Schulze et al. (Roussaki-Schulze et al., 2005) evaluated the presence of human papillomavirus in melanoma biopsy specimens and found that five of 28 (17.85%) biopsy melanoma specimens were positive for HPV DNA while HPV was not detected in any of the 6 biopsy specimens of the control group (0/6). The studies mentioned indicate to some extent that HPV might be related with the development of malignant melanoma.

Claims.

Null hypothesis:

Human papillomavirus and malignant melanoma are not causally related, both are independent of each other. $k = 0$.

Alternative hypothesis:

Human papillomavirus and malignant melanoma are causally related, both are not independent of each other. $k \neq 0$.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

La Placa et al. (La Placa et al., 2005) investigated the presence of HPV DNA and in malignant melanoma (MM) and detected of mucosal high-risk HPV genotypes in 14 of 51 melanoma specimens but not in any of the 20 biopsy specimens of the control group (0/20). are view by **Table 12**.

Table 12. The data of Hahn et al. (Hahn et al., 2008)

		Malignant melanoma B_t		
		Yes = +1	*No = +0*	*Total*
HPV DNA A_t	Yes =+1	14	**0**	14
	No = +0	37	20	57
	Total	51	20	71

The study of La Placa et al. (La Placa et al., 2005) provided highly significant evidence that HPV is causally related with malignant melanoma (p (IMP)=1, X^2 (IMP)=0.017857143, k =0.310353394, p value (k) = 0.008920547) itself. **Q. e. d.**

4. Discussion

The investigations evaluating the presence of human papillomavirus (HPV) in malignant melanoma specimens by polymerase chain reaction (PCR) technology have yielded very different detection rates. Some authors evidenced HPV to a high degree in malignant melanoma specimens while others did detect its presence to a very low degree. These published discrepancies in HPV detection (Terris et al., 1997) are to some extent due to the differences in primer sets utilized too. Still, especially the study of La Placa et al. (La Placa et al., 2005) provided significant evidence of a cause effect relationship (p (IMP)=1, X^2 (IMP)=0.017857143, k =0.310353394, p value (k) =0.008920547) between HPV and MM. A narrow emphasis on the small-sample settings as the primary focus of study design of the study of La Placa et al. (La Placa et al., 2005) can be misleading. Besides of the study of La Placa et al. (La Placa et al., 2005), Family history of malignant melanoma is causally related with HPV. Since malignant melanoma is not an inherited disease, the study of Le Marchand et al. (Le Marchand et al., 2006) indicates to the possibility of an infectious agent as the cause of malignant melanoma. Dréau et al. (Dréau et al., 2000) provided data which support the Null-hypothesis *without* HPV *no* malignant melanoma. The study of Dréau et al. (Dréau et al.,

2000) missed the control group and due to formal aspects cannot be used for causation analysis. Nonetheless, according to Dréau et al. (Dréau et al., 2000) *without* HPV *no* malignant melanoma. Roussaki-Schulze et al. (Roussaki-Schulze et al., 2005) provided significant evidence that HPV is a conditio per quam of malignant melanoma. The control group of Roussaki-Schulze et al. (Roussaki-Schulze et al., 2005) was inappropriate and the data were not considered for causal analysis. A few contradictory studies which investigated the involvement of HPV in melanoma are worth being mentioned. Ruer et al. (Ruer et al., 2009) used an inappropriate complementary wide excision of healthy skin as internal control and failed to detect the relationship between HPV and MM. In point of fact, Human papillomavirus (HPVs) is frequently (Hazard et al., 2007; Hsu et al., 2009) found in healthy skin which can lead to bias. In toto, one single study is too less to establish a generally valid conclusion concerning the relationship between HPV and MM. However, the results of the study of La Placa et al. (La Placa et al., 2005) are convincing and the role of HPV in the development of malignant melanoma does not remain speculative any longer. A low cost and highly effective vaccination against HPV will prevent from malignant melanoma.

5. Conclusion

This review suggests that UV radiation probably has effect or little on malignant melanoma. Evidence in this context was insufficient to allow any firm conclusions. Several of the studies considered provided self-contradictory data and none of the studies included provided significant evidence of a causal relationship between UV radiation and malignant melanoma. In addition, several high-tech studies point to a possible infectious agent (HPV) as the cause of malignant melanoma. In particular, according to the study of La Placa et al., human papilloma virus is a cause of malignant melanoma (p (IMP)=1, X^2 (IMP)=0.017857143, k =0.310353394, p value (k) =0.008920547). The result of this investigation does not justify the position to ignore a possible cause-effect relationship between human papillomavirus and malignant melanoma. A very careful and more systematical study with a greater sample size is justified to prove the possible cause effect relation-ship between human papillomavirus and malignant melanoma. Until a better explanation can be provided, human papillomavirus is the cause of malignant melanoma.

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