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La chaleur d'origine extracorporelle constitue-t-elle un risque de cancer testiculaire ? Revue systématique et méta-analyse

Are extracorporeal body sources of heat a risk for testicular cancer ? A systematic review and meta-analysis

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I. INTRODUCTION

A. Context

This thesis focuses on male contraception, a real public health issue as men want to be involved more and more in contraceptive methods.(1)

In 2017, a new male contraceptive method was created by Maxime Labrit: the Andro-switch ring.(2) This silicone ring suspends the testicles in contact with the pubis, which exposes the testicles to body temperature, around 36-37°C. Recently, in 2022, a meta-analysis(3) has demonstrated that heat-induced stress leads to a reduction in sperm count and quality. The contraceptive effect of AndroSwitch is therefore based on an induced increase in testicular heat. But what about the side effects of this method?

In December 2021, the commercialization of the AndroSwitch method was suspended in France by the French National Agency for the Safety of Medicines and Health Products (ANSM), because it did not have the CE *(Conformité Européenne)* marking yet, which is a European marking guaranteeing sufficient efficacy and safety.(4)

To return on the market, the contraceptive ring needs to be scientifically validated. Overall, the concept of thermal male contraception needs to be studied in order to determine the potential adverse effects over the long-term, particularly since heat is already known to be at higher risk of infertility disorders. Some studies about fertility disorders showed that induced heat exposure to the testicles(5)(6)(7) lead to a decrease in spermatogenesis at first, but after 4 to 8 months' cessation of heat exposure, lead to a reversibility of spermatogenesis. These findings suggest a reversibility of the male contraception method.

Thus, through a systematic review of the literature, the aim of this thesis is to investigate the link between testicular heat exposure and testicular cancer, which may be a possible adverse effect of male thermal contraception methods.

B. Epidemiology of testicular cancer

According to the French National Cancer Institute, testicular cancer accounts for around 1% of cancers in men. It is the most common cancer among young men, with most cases diagnosed between the ages of 25 and 35.(8) The worldwide incidence of testicular cancer has increased over the past 30 years, particularly in industrialized regions such as North America, Europe and Oceania.(9) Mortality has also risen, but the incidence/mortality ratio is decreasing, probably due to improvements in cancer diagnosis and treatments.(10) The prognosis is excellent though, with a cure observed in 95% of cases.(11)

The three most common histological types are seminoma, mixed nonseminomatous germ cell tumors and embryonal carcinomas.(8) Regarding treatments, seminomas and nonseminomas react differently. Treatment for stage I seminoma consists of orchiectomy and irradiation of the subdiaphragmatic lymph nodes, with response rates close to 100%, while early-stage non-seminomas are cured by orchiectomy alone. For the metastatic stage, the bleomycin-etoposide-cisplatin chemotherapy regimen is the most widely used.(12)

The etiologic factors of testicular cancer have been largely studied in recent decades. Some risk factors for testicular cancer have been explored, but the most important risk remains a medical history of cryptorchidism.(13)(14)

- Risk factors that may be associated with testicular cancer: cryptorchidism, genetic (brothers, father-sons), age (between 25-35 years and around 80 years), prematurity, nulliparity, high androgen levels, ethnic populations of Caucasian origin, month of birth (mostly in August), placental retention, presence of "Rh" antibodies, fetal presentation, human carcinogens (dimethylformamide, nitrogen-rich fertilizers, phenols, pesticides), occupations (leather tanners, aircraft repairers, firefighters), father's occupations (fixed engineers, woodworking, metalworking, food processing, catering), adult height, congenital and developmental anomalies of the testicles (low sperm count, infertility, atrophic testicles), history of testicular cancer in the contralateral testicle, dietetic (fat, milk, cheese, meat, few vegetables, little calcium)
- Risk factors that may be protective against testicular cancer: late puberty, having several children, non-Caucasian ethnic population (androstenedione and testosterone levels are higher in mothers with black skin).

Exposure to heat as a risk factor for testicular cancer has been studied in the past, but studies are few and discordant. In 2014, the US National Cancer Institute stated that evidence was not sufficient for heat exposure as a risk factor for testicular cancer, and that further investigation was needed.(14) It should also be noted that no systematic review of the literature has yet been carried out on this subject.

II. GENERALITIES

A. Definitions and notions about heat exposure

Definitions about heat exposure are essential for understanding the effects of heat on the body.(15)

- **Temperature** is defined as the average kinetic energies of the molecules in a material.
- **Internal energy** is defined as the total energy of all molecules inside the object.
- **Heat** (with symbol Q, unit Joule) is defined as the total amount of energy that flows from one body to another spontaneously because of their temperature difference. When there is a temperature difference, heat flows spontaneously from the hottest system to the coldest.
- **Thermodynamic equilibrium** is a concept implying that when two objects are brought into thermal contact, heat flows between them until they come into equilibrium.
- **Heat balance** is the sum of heat flows produced by the body and heat flows exchanged with the environment. Hypothermia occurs when the heat balance is negative, and hyperthermia when the heat balance is positive. The formula is as follows : M + P + C + R + E = 0 Kcal / m2 / hour (with *M= heat production by metabolism, P= heat loss by Conduction, C= heat loss by Convection, R= heat loss by Radiation, E= heat loss by Evaporation*)
- **Wet bulb temperature (WBGTcrit)** is a validated index that represents the temperature above which the human body is unable to regulate core temperature (Tc), known as the "heat stress" temperature. This index considers ambient temperature, relative humidity (RH) and radiant heat for outdoor conditions. The threshold decreases as humidity increases because humidity contained in hot environments prevents sweat from evaporating. Death occurs after six hours at 35°C wet-bulb temperature at 100% WGBT, even in healthy young adults.(16)
- **Threshold Limit Values (TLV)** is a threshold commonly used to protect workers against occupational heat stress. It comes from the ACGIH (*American Conference of Governmental Industrial Hygienists*) guideline. The aim is to limit the increase in workers' core temperature (Tc) to less than -1°C or 38°C max over a standard 8-hour shift. TLVs are determined on the basis of two main factors : ambient temperatures and the estimated metabolic work rate. Other correction factors exist, such as the clothing adjustment factor (CAF).(17)
- **Heat related work** : the CSST (*Commission de la Santé et de la Sécurité du Travail*) defines heat at work as any work performed in conditions >30°C for sedentary activity, and >28°C for physical activity.(18)

B. Anatomo-physiology of the testicles

The testicles are the male reproductive organs and have two main roles: to produce sperm and to produce male hormones. Regarding adult men, the testicles measure around 5cm long and 3cm wide, and are each contained in an external compartment called the scrotum or bursa, which is under and in front of the perineum.

The testicle is surrounded by numerous thin envelopes (scrotal skin, dartos fascia, external spermatic fascia, cremasteric muscle, internal spermatic fascia, vaginal membrane, mesorchium). Attached to the upper and posterior part of the testicle is the epididymis which contains all the seminiferous tubules in which the spermatozoa are created and transported. The efferent ducts end in the convoluted vas which is 40cm long and extends from the epididymis of the testicle to the ejaculatory duct of the prostate. The ejaculatory duct also contains the seminal vesicles, which are sperm reservoirs where sperm accumulates between successive ejaculations.(19)

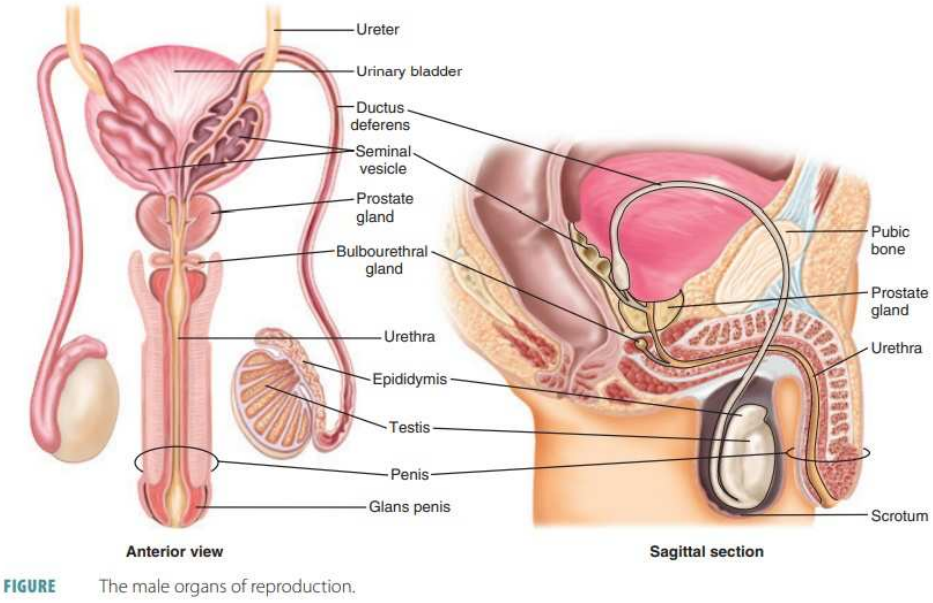


FIGURE The male organs of reproduction.

Male reproductive system(19)

C. Thermoregulation

A) Thermoregulation of the body

Human beings are homeotherms.(19) This means that the energy of their metabolism depends on the ambient temperature. This metabolism should remain constant in the thermal neutral zone, but when the ambient temperature becomes lower or higher than the thermal neutral zone, the metabolism is regulated by thermogenesis and thermolysis mechanisms.

This regulation enables the body temperature to be maintained between 35.7°C and 37.3°C, with an average body temperature of around 36.5°C.
Several components are involved in the body heat regulation pathways(21):

- Thermosensors: found in the hypothalamus, the spinal cord, the abdomen, the muscles, the blood vessels and the dermis, their role is to relay the body temperature information to the hypothalamic integrating center.
- Hypothalamic thermoregulatory center: once the information has been received and analyzed, activation signals are sent to the thermoregulatory effectors. There is a system that tolerates temperature variations of 1 to 2°C. This is known as the "caloric buffer capacity".
- Thermoregulatory effectors: they make thermoregulatory phenomena possible such as thermogenesis and thermolysis. Effectors are essentially represented by the sweat glands, arteriovenous circulation, and muscles.

There are three main mechanisms for thermogenesis (intrinsic heat production mechanism):

- Basic metabolism: this is the body's heat production at the temperature of thermal neutrality. This is the heat released by the vital functioning of the cells. Its production is about 1700 Kcal/h for a 70 kg fasting man at rest.
- Muscle contraction: this is the main source of heat production. At rest, heat production is 70 Kcal/h. During exercise, this production is multiplied by 8.
- Vasoconstriction: it allows heat to pass from the peripheral zones to the central zone of the body to help in the functioning of vital organs (brain, heart).

There are four main mechanisms for thermolysis (heat loss mechanism), facilitated by vasodilation of the blood vessels:

- Conduction: heat transfer from the body to a solid by direct contact
- Convection: heat transfer from the body to a liquid
- Radiation: heat transfer from the body to the surrounding air via emissions of electromagnetic waves
- Evaporation: heat transfer from a liquid to a vapor via the sweat glands located in the skin. Sweating is the main mean of thermolysis in the human body.

Another poorly understood mechanism for thermoregulation is the thermoregulatory behaviour.(22) Studies on rats have shown that they instinctively have heat-regulating behaviours, such as burrowing, huddling, postural extension, or moving towards nearby sources of heat.(23) We therefore assume that thermoregulatory behaviours are driven by the motivational systems that derive from physiological needs, such as eating and drinking.

B) Thermoregulation of the testicles

In order to work properly, testicular temperatures have to be maintained 2-8°C below body temperature.(24) In fact, testicular heat is between 31°C and 36°C depending on methods of measuring heat and the absence or presence of pathologies.(25)
To maintain this thermal condition, there are testicular heat regulating systems(26):

- Scrotum: it is a thin cutaneous envelope that has natural heat loss properties thanks to its physical characteristics : it has no subcutaneous fat (mainly brown and beige fat, which can increase local heat)(27) and it probably contains apocrine glands that enable the sweating mechanism(28), although this is still questioned in humans. Activation of the heat receptors would occur at a specific threshold(29)(30).
- Dartos and cremasteric muscles: they efficiently respond to changes in ambient temperature, thanks to their contraction/relaxation abilities.
- Pampiniform plexus: this plexus is located in the spermatic cord. It is a site of heat exchange between the arterial blood entering via the tortuous testicular artery and the venous blood leaving via the multiple veins surrounding it, allowing pre-cooling of the arterial blood that comes from the testis.(31)(32).

D. Physiopathology of heat exposure on the body and the testicles

A) Effects of heat exposure on the body

Numerous studies have been carried out to understand the effects of heat on the human body, particularly in occupations most exposed to heat.(33)(34) The increase in core temperature >38°C leads to psychomotor changes. If left untreated, there is a decline in intellectual capacity followed by paresthesia, sometimes leading to death in the most severe forms. The organs most affected are the brain and liver.

Three levels of heat-related clinical severity can be observed(35):
Slight symptoms (core temperature > 38.3°C):

- **Heat oedema**: linked to intracellular dehydration associated with interstitial hyperhydration, oedema starts in the feet and ankles after a week's exposure to the heat.
- **Heat cramps**: these are linked to an ionic disorder, chlorine deficiency. It causes tetany, which worsens if the patient continues to drink without absorbing salts. The first muscles affected are the abdominal, quadricipital and gastrocnemius muscles.
- **Skin disorders**: it begins with redness of the skin associated with vasodilatation of the vessels (thermolysis), and can progress to a red miliaria, which is a skin rash associated with insufficient sweating (especially on the neck, groin and trunk).

Moderate symptoms (core temperature between 38.3°C and 40°C):

- **Heat-induced dizziness**: it is linked to a significant vasodilation of cerebral vessels
- **Heat exhaustion**: it includes asthenia, tachycardia, intense thirst, vomiting, diarrhoea, headache. If the patient doesn't receive immediate care, the condition rapidly deteriorates into heat stroke.

Severe symptoms (core temperature > 40.5°C):

- **Heat stroke**: it gives symptoms similar to heat exhaustion, with the addition of neurological disorders (confusion, convulsions, coma), hypotension and hyperventilation. Patients who survive the neurological phase of heatstroke has a higher risk of rhabdomyolysis, acute respiratory distress syndrome, compartment syndrome, liver dysfunction, acute renal failure, electrolyte abnormalities or disseminated intravascular coagulopathy. Emergency cooling techniques consist in placing the individual in cold or iced water for 10 to 15 minutes, then with a cold damp towel during medical transport to the hospital. Mortality rates increase with the duration of hyperthermia.

B) Effects of heat exposure on the testicles

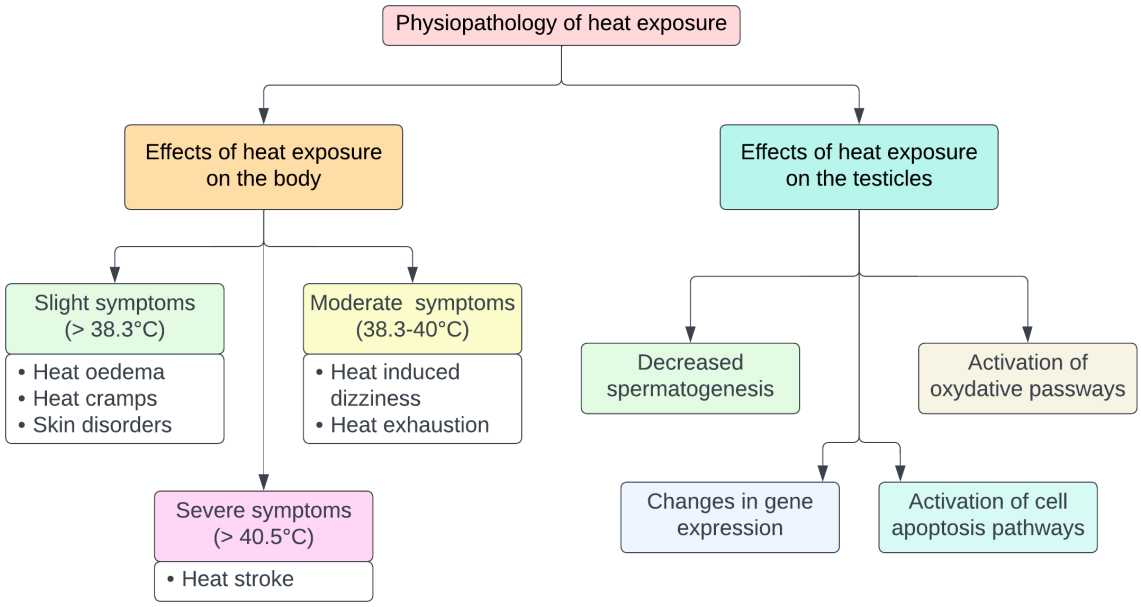
Heat can cause several damages on the testicles(36):

- **Decreased spermatogenesis:** spermatogenesis is the process of sperm production and involves a complex series of steps to produce functional sperm. It takes place in the seminiferous tubules of the testicle and lasts approximately 74 days. The process of spermatogenesis ideally occurs 2°C below the core body temperature.(37) As early as 1922, Crew and his team suggested that exposure of the testicles to heat could lead to a reduction in spermatogenesis.(38) The temperature-dependent relationship on spermatogenesis which has been demonstrated(39) in the 1960s was followed by numerous studies focusing on the link between heat and infertility. In 2022, a meta-analysis(3) demonstrated that heat-induced stress reduced sperm count and quality.
- **Changes in gene expression**: gene expression can be modified due to heat stress, especially genes coding for cell arrest and increased apoptosis (HSF1, p53, caspases). It may also inhibit genes coding for cell repair (Bag-1, RNA-binding proteins Cirp, DNA polymerase β and DNA ligase III). It should be noted that after a few hours of heat stress, some pro-apoptotic genes can be down-regulated to prevent the destruction of all the cells.(40)
- **Activation of oxidative pathways**: The oxidative balance in cells is linked to pro-oxidant mechanisms counterbalanced by anti-oxidant mechanisms.(41) The main pro-oxidant mechanism involves the production of Oxygen Radical (or Reactive) Species, known as ROS. By definition, these free radicals are chemical species with a single electron on their peripheral stratum, making them extremely unstable and highly reactive. They contribute to DNA, protein and lipid damage. To maintain these radicals at an acceptable level, natural antioxidants are present in the testicles (vitamins C,

vitamin E and carotenoids). When this oxidative balance is disrupted, oxidative stress results in cell apoptosis and sperm dysfunction.(42) There are two likely ways in which ROS could be involved in the response to heat stress(43) : a direct activation of apoptosis by oxidation of cellular components such as DNA and lipids, and an indirect activation of apoptosis by regulatory pathways activated by ROS.

- **Activation of cell apoptosis pathways**: exposure of testicular germ cells to heat stress can cause changes in gene expression, DNA damages or autophagy programmed by the cell leading to cell apoptosis. The apoptosis effector proteins (caspases 3,6,9) can be activated by two signaling pathways(25) : an intrinsic pathway depending on the mitochondria and the Bax/Bcl2 proteins, and an extrinsic pathway depending on the cellular membrane and the Fas/FasL proteins.

This scheme summarises the consequences of testicular heat stress on the body and on the testicles:



Physiopathology of heat exposure

III. ARTICLE

Title: Are extracorporeal body sources of heat a risk for testicular cancer ? A systematic review and meta-analysis
Main authors: CARTON C., MIGNOT S.
Registration on PROSPERO: 17/09/2023 with the following ID: CRD42023464097

A. Introduction

The global incidence of testicular cancer has increased over the past 30 years, particularly in industrialized regions such as North America, Europe and Oceania.(9) Testicular cancer is a rare disease, representing about 1% of all cancers among men. It occurs mainly between the ages of 25 and 35 years old, making testicular cancer the most common solid malignancy in young men.(8) It has a good prognosis, with a five-year survival rate reaching 90% in the 2000s. Testicular cancer risk factors have been identified such as cryptorchidism(44), the presence of a contralateral testicular tumor(45), high socioeconomic status(46) or some occupations such as agricultural workers, construction workers, firemen, policemen, military personnel, as well as workers in paper, plastic or metal industries.(47)

Exposure to heat as a risk factor for testicular cancer has been studied in the past, but studies were few and discordant. In 2014, the American National Cancer Institute considered that further investigation was needed.(14) The subject is even more interesting with the development of male thermal contraception methods. In fact it is becoming a real public health issue as men want to be more and more involved in contraception.(1) The first experimental contraception device started in the 1980s and kept improving until the recent Androswitch ring in 2017. However, none of the male contraception devices has obtained the CE (*Conformité Européenne*) marking yet, which is a European marking guaranteeing efficacy and safety of a device.(4)

Through a systematic review of the literature, this study aims at determining a potential link between a prolonged testicular exposure to supra-physiological temperatures and an increased testicular cancer risk.

B. Methodology

Outcomes:

Main outcome of the study was defined by testicular cancer prevalence or incidence or association with any type of heat exposure. The measures of effect used were odds ratios (OR), relative risks (RR), hazard ratios (HR), and standardised incidence ratios (SIR). Testicular cancer diagnoses were defined by an evocative imagery, or an evocative anatomopathology, or data from an institutional cancer registry.

Population, comparators, type of studies:

The population was composed of all men without age criteria, and the comparator was the general male population. Studies included in the analyses were original papers (retrospective studies, cohorts, case-control studies, cross-sectional studies, epidemiological studies), excluding case reports.

External heat exposures:

The concept of heat being large, we had to determine the heat exposure factors for the inclusion criteria. A systematic review from 2009 showed a significant association between infertility and testicular cancer.(48) Therefore, in our study, we used the testicular heat exposures explored in infertility studies. We also chose to study occupational exposures to heat, defined either if they increase central temperatures, or defined by the *CSST (Commission de la Santé et de la Sécurité du travail)* as any work carried out in conditions >30°C for sedentary activity, and >28°C for physical activity.(18)

All together, we selected four types of heat exposures(49):

- Clothing increasing testicular temperatures: two studies from 1982(50) and 2013(51) demonstrated that wearing clothing increased the scrotal temperature by +1.5-2°C compared to the state of nudity, whatever the position. This increase in temperature would be linked to a thermal insulation mechanism creating a reduction in air exchange and therefore difficulties in evaporating testicular heat. We then selected “wearing tight clothing”(52)(53), “soiled diapers covered in plastic”(54)(55), and “occupational cyclists'' often wearing tight Lycra outfits.(56)
- Prolonged sitting position: sitting appears to be a risk factor for supraphysiological increases in testicular temperatures, probably due to the rise of testicular heat in contact with the thighs and therefore in contact with body heat. In 2005, a study(52) found that scrotal temperatures during a 45-minute sitting period were significantly higher by +1.5-2.28°C than during walking, regardless of the types of studied underwear. Additionally in 2007, a study(51) added that sitting with legs crossed leads to an increase in scrotal temperature compared to sitting with legs apart. We then selected “sitting position > 4 hours/day usually or continuously > 2 hours/day”(57) (but not “sedentary work” which is a too much larger concept), “occupational drivers” (more precisely car drivers(58)(59) and airplane pilots who often remain seated for long hours), and “people in a wheelchair for > 7 months”.(60)
- Testicular contact to external hot sources: we selected “sauna for > 20 minutes at a temperature > 80°C”(61)(62)(63), “hot baths for > 30 minutes per week for > 3 months at a temperature > 37°C”(64)(65), and “use of a laptop on lap for > 60 minutes”.(66)
- Occupational heat exposures: occupational heat exposures were studied as a potential etiology for infertility(67). We selected “underground minors”(68), “welders and foundry workers in metal industries”(69), “oven operators”(70), “bakers”(71)(72), and “submariners”.(73)

Database, extraction data, bias assessment, analysis:

Database: the search queries came from 8 databases (PubMed, Embase, Cochrane, Web of Science, Sudoc, Google Scholar, Lissa, CisMEF) and are disponible on PROSPERO registration.

Screening: RAYYAN program was used for the selection of articles. Data from the search queries were screened independently with a double-blind strategy, by a first selection on titles and abstract, then by a second selection on full texts, according to the predefined inclusion and exclusion criteria shown in Table 1. If any disagreement on whether to include a specific study, it was sold by a discussion between all reviewers. LUCIDCHART software was used for the Flow chart presentation.

Data extraction: EXCEL software was used for data extraction. If necessary, another team member could check the extracted data to ensure the quality of extraction. Based on PRISMA recommendations, data extracted included: study information (authors, title, date of publication, country, funding), methodology (study design, characteristics and details of population, randomization method, characteristics of exposition, follow-up), results (informations about our main outcome), and additional data if relevant.

Quality assessment: analyzed articles appeared to be only non-randomized cohorts and case-control studies. Thus, The NewCastle Ottawa (NCO) was used as proposed by Cochrane as an alternative to the ROBINS-1 tool.

Analysis: LUCIDCHART software was used for the Flow chart. Results were presented in a general Table. A narrative analysis (qualitative analysis) was made from significant results data according to types of studies, types of results and types of heat exposure (clothing increasing testicular temperatures, prolonged sitting position, testicular contact to external hot sources, and occupational heat exposures). Two meta-analysis (quantitative analysis) were made from significant results according to types of studies, types of results, and quality of studies. JAMOVI software was used for meta-analysis.(74)(75)(76)

Table 1: Inclusion/exclusion criteria

Inclusion criteria	**Exclusion criteria**
-Main outcome: testicular cancer prevalence or incidence or association with any type of heat exposure **- External heat exposures:** . Clothing increasing testicular temperatures: wearing tight clothing, soiled diapers covered in plastic, professional cyclists . Prolonged sitting position: sitting position > 4h/day habitually or continuously >2 h/day, occupational drivers (car drivers or airplane pilots), people in a wheelchair for >7 months . Testicular contact to external hot sources: sauna for >20 minutes at a temperature > 80°C, hot baths for >30 min per week for >3 months at >37°C, use of a laptop for >60 min . Occupational heat exposures: underground minors, welders and foundry workers in metal industries, oven operators, bakers, submariners **-Population**: healthy men without age criteria **-Comparator**: general male population	**-Population**: men with a described disease, women, animals **-Studies**: . Not an original paper (review, meta-analysis, letter), case report . Full text in a language other than English or French

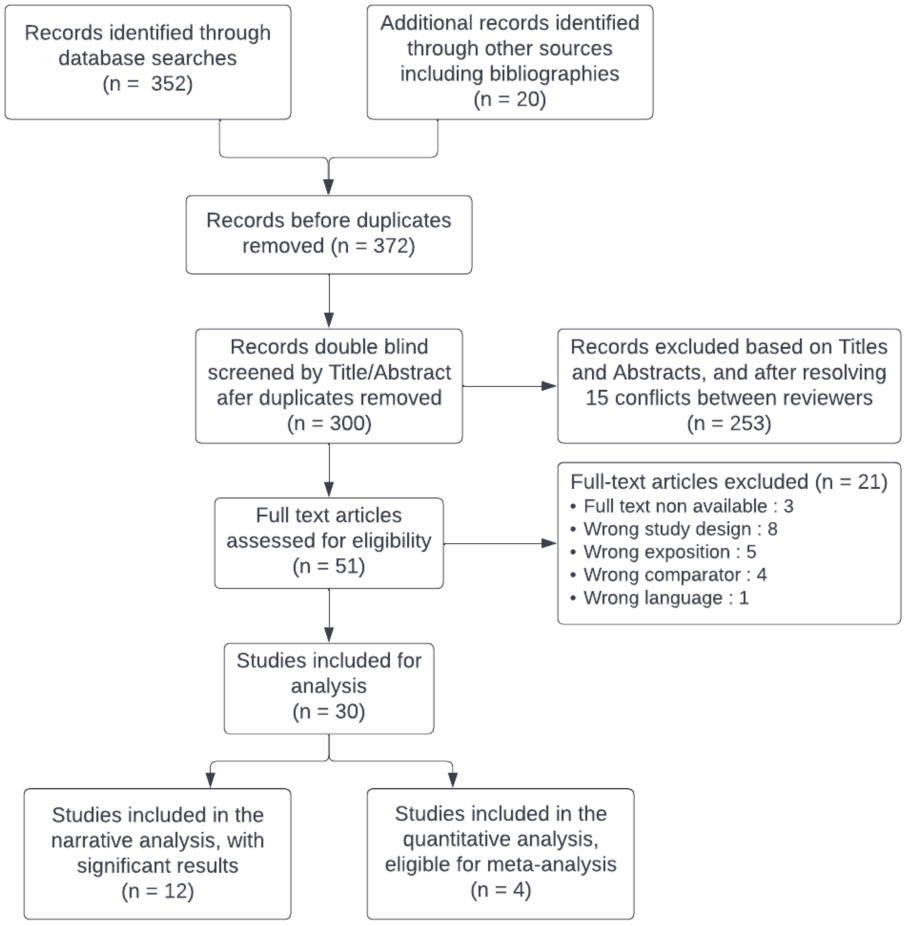
C. Results

Screening :

Results from search queries came to 352 articles, among which 130 duplicates (87 articles from Pubmed, 136 articles from Embase, 23 articles from Cochrane, 93 articles from Web of Science, 8 articles from Sudoc, 5 articles from Google Scholar, 0 article from Lissa, 0 article from CisMEF). In addition to this, there were 20 articles added to the analyses through other resources, for a total of 372 articles.

After the first screening (by Title and Abstract) it remained 51 articles. After the second screening (after reading Full texts) it remained 30 articles, from which 12 articles with significant results were included in the narrative analysis and 4 articles were eligible for meta-analysis (*Figure1*).

Figure 1: Flow chart



All results from primary analysis:

All results are summarized in tables following extraction data from the 30 included articles: 18 were non randomized cohort studies (*Table 2*) and 12 were case-control studies (*Table 3*).

Table 2 : Non randomized cohort studies (18 studies)

Title of the article. Main author. Publication year.	Study type. Comparator(s).	Heat exposure (+/- exposure duration)	Main outcome results (testicular cancer)
1) Cancer incidence among Norwegian airline pilots Articles. Tor Haldorsen, MSc. 2000.	Retrospective cohort study (70 560 person-years male commercial pilots). Comparator was the national rate.	Commercial pilots (exposure time not cited)	SIR = 1.5 (IC95% = 0.7-2.6)
2) Cancer Incidence and Mortality Among Fighter Aviators in the United States Air Force. Niklas Hammar. 2002.	Cohort (34 976 fighter aviators). Comparator was the general US population.	**Fighter aviators (pilots and backseat aircrew)**	**RR = 0.38 (IC95% = 0.27-0.51)**
	Cohort (34 976 fighter aviators). Comparators were the other officers.	**Fighter aviators (pilots and backseat aircrew)**	**RR = 1.30 (IC95% = 1.01-1.93)**
3) Cancer incidence in airline and military pilots in Sweden 1961–1996. Niklas Hammar. 2002.	Cohort (4298 male civil aircraft pilots (n=1490) and military pilots and navigators (n=2808)). Comparator was the general male population of Swedish.	All pilots (at least 2 years)	SIR = 1.55 (IC95% = 0.62-3.18)
4) Cancer incidence in Republic of Bulgaria aircrew, 1964-1994. Milanov L. 1999.	Cohort (52 963 men of Republic of Bulgaria Air Force and civil aviation aircrew). Comparator was the general male population of the Republic of Bulgaria.	All pilots (at least 1 year)	SIR = 2.51 (IC95% = 0.9-4.92)
5) Cancer incidence in the Western Australian mining industry (1996–2013). Nita Sodhi-Berry. 2017.	Epidemiological cohort (153,922 miners, 85.7% male). Comparator was the general Western Australian population.	All miners (at least 1 months, or 3 months per year, mean duration work was 6.6 years)	SIR = 0.90 (IC95% = 0.73-1.07)
6) Cancer incidence in the United States Air Force aircrew, 1975-89. Grayson, JK. 1996.	Cohort (532 981 man-years of US Air Force officers on active duty). Comparator was from the National Cancer Institute SEER program.	Military pilots (at least 1 year)	SIR = 1.04 (IC99% = 0.72-1.44)
7) Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. Pierre R Band. 1996.	Cohort (2 740 Air Canada pilots, 62 449 person-years). Comparator was the Canadian general population.	Pilots (at least 1 year)	SIR = 0.63 (IC90% = 0.11-1.98)
8) Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. Eero Pukkala. 2002.	Cohort study (10 032 male airline pilots, 177 244 person-years). Comparator was the national rate.	Pilots (main occupation, exposure time not cited)	SIR = 1.11 (IC95% = 0.69-1.70)
9) Incidence of Testicular Cancer and Occupation among Swedish Men Gainfully Employed in 1970. Marina Pollán. 2001.	Historical cohort (31 668 842 person-years of Swedish men who were gainfully employed at the time of 1960 and 1970 census). Comparator was the total cohort.	Mining and quarrying (main occupation, exposure time not cited)	Seminomas : RR = 1.03 (IC95% = 0.38-2.75)
		Metal annealer, temperer - main occupation (exposure time not cited) - at 1960 and 1970 census (> 10 years of work)	**Seminomas : RR = 5.85 (IC95% = 1.88-18.20)**
			Seminomas : RR = 21.89 (IC95% =7.04-68.06)
		Metal caster and moulder (main occupation, exposure time not cited)	Seminomas : RR = 1.55 (IC95% = 0.5-4.83)
		Other metal processing worker - main occupation, exposure time not cited) - at 1960 and 1970 census, more than > 10 years of work)	Seminomas : RR = 1.14 (IC95% = 0.57-2.28)
			Seminomas : RR = 1.10 (IC95% = 0.35-3.42)
		Construction smith - main occupation (exposure time not cited) - at 1960 and 1970 census (more than > 10 years of work)	Seminomas : RR = 1.81 (IC95% = 0.81-4.05)
			Seminomas : RR = 3.29 (IC95% = 1.06-10.22)
10) Incidence of testicular cacner in U.S. AirForce officer aviators : 1998-2008. Christopher Walker. 2011.	Retrospective cohort study (of US AirForce male aviators and non-aviators officers). Comparator was the nonflyer officers.	Aviators (average flight time was 843.0 h)	Incidence rate = 16.9 cases / 100,000 and RR = 2.15 (IC95% = 0.67- 6.89)

11) Malignancy in U.S. Air Force fighter pilots and other officers, 1986–2017: A retrospective cohort study. Anthony S. Robbins. 2020.	Retrospective cohort study (of 88 432 US Air Force service members). Comparator was the other commissioned officers.	Force fighter pilots	TRI = 0.92 (IC95% = 0.56–1.52)
12) Mortality and cancer incidence in a cohort of commercial airline pilots. Pierre R. Band. 1990.	Cohort (18 060 person-years of male pilots employed by Canadian Airlines International). Comparator was the British Columbia population.	Commercial pilots (at least 1 year)	SIR = 1.75 (IC90% = 0.3-5.5)
13) Workers in Australian prebake aluminium smelters: update on risk of mortality and cancer incidence in the Healthwise cohort. Del Monaco A. 2023.	Cohort (4507 male employees in prebake aluminium smelters, 121700 person-years). Comparator was the general Australian population.	All smelters (at least 3 months, until 27 years)	SIR = 1.15 (IC95% = 0.57-2.06)
14) Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among Finnish workers exposed to diesel or gasoline engine exhaust. Johannes GUO. 2004.	Cohort (30 million person-years of economically active Finns). Comparator was the general Finnish population.	Locomotive drivers	SIR = 0.71 (IC95% = 0.02-3.95)
		Bus drivers	SIR = 0.65 (IC95% = 0.13-1.89
		Taxi drivers	SIR = 0.41 (IC95% = 0.01-2.26)
		Truck drivers	SIR = 1.35 (IC95% = 0.76-2.23)
		Motor vehicle or tram drivers	SIR = 1.03 (IC95% = 0.49-1.89)
15) Study of cancer incidence among 8530 male workers in eight Norwegian plants producing ferrosilicon and silicon metal. Ånund Hobbesland. 1999.	Historical cohort study (8 530 metal workers, 193 930 person-years). Comparator was the general Norwegian population.	**Furnace workers (at least 6 months)**	**SIR = 2.3 (IC95% = 1.05-4.37)**
16) Testicular Cancer, Occupation and Exposure to Chemical Agents among Finnish Men in 1971-1995. Johannes Guo. 2005	Cohort (667 121 of all economically active Finnish men, 19.7 million person-years). Comparator was the general Finnish male population.	Truck drivers (main occupation, exposure time not cited)	RR = 1.4 (IC95% = 0.8-2.3)
17) Time trends and occupational variation in the incidence of testicular cancer in the Nordic countries. Outi Ylönen. 2018.	Epidemiological study (26 million inhabitants of the five Nordic countries : Denmark, Finland, Iceland, Norway, Sweden). Comparator was the general population of the Nordic countries.	Mining	Seminomas : SIR = 0.86 (IC95% = 0.52–1.35) Non-seminomas : SIR = 0.47 (IC95% = 0.13–1.19)
		Drivers	**Seminoma : SIR = 0.88 (IC95% = 0.77–1.0)** Non-seminomas : SIR = 1 (IC95% = 0.85–1.19)
		Smelting workers	Seminomas : SIR = 0.86 (IC95% = 0.66–1.12) Non-seminomas : SIR = 0.74 (IC95% = 0.50–1.05)
		Welders	Seminomas : SIR = 0.74 (IC95% = 0.53–1.01) Non-seminomas : SIR = 0.82 (IC95% = 0.48–1.31)
18) Work-related cancer in the Nordic countries. Andersen A. 1999.	Cohort (10 millions included). Comparator was the general population of the Nordic countries.	Mining	SIR = 0.73 (IC95% = 0.38-1.27)
		Drivers (of cars, taxis, vans, buses, motorcycles, trams, and light and heavy trucks)	**SIR = 0.8 (IC95% = 0.69-0.92)**
		Smelter and metal foundry workers	**SIR = 0.78 (IC95% = 0.6-1.0)**
		Welders	SIR = 1.02 (IC95% = 0.73-1.4)

Table 3 : Case-control studies (12 studies)

Title of the article. Main author. Publication year.	Study type. Comparator(s).	Heat exposure (+/- exposure duration)	Main outcome results (testicular cancer)
19) Case–Control Study of Male Germ Cell Tumors Nested in a Cohort of Car-Manufacturing Workers: Findings From the Occupational History. Ingo Langner. 2010.	Case-control study nested in a cohort of car-manufacturing workers (205 cases, 1105 controls). Comparator was the workers in the same factories as the cases for at least 6 months.	Plumbers, welders, sheet and structural metal workers (at least 6 months)	OR = 1.4 (IC95% = 0.99–1.95)
		"welders and flame-cutters" only	**OR = 1.57 (IC95% = 1.06-2.34)**
		Miners (at least 6 months)	OR = 1.7 (IC95% = 0.33-9.24)
		Metal producers (at least 6 months)	OR = 0.7 (IC95% = 0.33-1.48)
		Blacksmiths, toolmakers and machine-tool operators (at least 6 months)	OR = 1.0 (IC95% = 0.75-1.44)
		Manufacturing of fabricated metal products (at least 6 months)	OR = 1.3 (IC95% = 0.71-2.48)
20) Case-control study on risk factors for testicular cancer. Lennart Hardell. 1998.	Case-control study (148 cases and 314 controls). Comparator was the general Swedish population.	Drivers (main occupation, exposure time not cited)	OR = 1.4 (IC95% = 0.9-2.4)
		Metal-worker (main occupation, exposure time not cited)	OR = 1.1 (IC95% = 0.6-2.0)
		Steelwork workers (main occupation, exposure time not cited)	OR = 1.0 (IC95% = 0.4-2.8)
		Welders (main occupation, exposure time not cited)	OR = 0.9 (IC95% = 0.5-1.6)
21) Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Margaret R KARAGAS. 1989.	Case-control study (323 cases, 675 controls). Comparator was the white males between 20 and 69 years of age randomly selected in the same area.	Underwear tight (jockey, designer) (usually worn)	RR = 1.1 (IC95% = 0.8-1.5)
		Long underwear use (also called long johns or thermal underwear, usually worn during cold weather) (for 0, 1-3, and >3 months)	RR (0 month) = 1 RR (1-3 months) = 1.1 (IC95% = 0.8-1.4) RR (> 3 months) = 1.5 (IC95% = 0.9-2.6)
		Heat-resistant clothing (usually worn)	RR = 0.9 (IC95% = 0.3-2.8)
		Hot tub or sauna use (for 0 month, 2-6 months, and >6 months)	**RR (1 month) = 0.5 (IC95% = 0.4-0.7) RR (2-6 months) = 0.5 (IC95% = 0.3-0.8) RR (> 6 months) = 0.5 (IC95% = 0.3-0.8)**
22) Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. Marie Walschaerts. 2007.	Case-control study (229 cases and 800 controls). Comparator was the partners of pregnant women receiving prenatal care in the same hospitals than the cases (healthy men aged 20-45 years).	Employment in metal trimming (main occupation, exposure time not cited)	Multivariate analysis : OR = 1.49 (IC95% = 0.53–4.15)
		Employment in welding ((main occupation, exposure time not cited)	Multivariate analysis : OR = 1.49 (IC95% = 0.53–4.15)
		Foundry work (main occupation, exposure time not cited)	Multivariate analysis : OR = 0.9 (IC95% = 0.25-3.22)
23) Is testicular cancer an occupational disease ? A case-control study of Royal Naval Personnel. S J Ryder.1997.	Case-control study (110 cases and 440 controls). Comparators were randomly selected from the Royal Navy.	Aircrew including pilots and observers (exposure time not cited)	OR = 1.07 (IC95% = 0.19-5.94)
		Submariners (exposure time not cited)	OR = 1.18 (IC95% = 0.68-2.08)

24) Military occupation and testicular germ cell tumour risk among US Air Force servicemen. Christina Denic-Roberts. 2023.	Nested case–control study (530 cases and 530 matched controls of active duty USAF servicemen). Comparator was the USAF servicemen who had no history of any malignancies except for non-melanoma skin cancer.	**Pilots (including pilot trainees)**	**OR=1.78 (IC95% = 1.06–3.01)**
		Fighter pilots	OR = 2.73 (IC95% = 0.96–7.72)
25) Occupation and risk of germ cell testicular cancer by histologic type in Ontario. Knight, JA; Marrett, LD; Weir, HK, 1995.	Case-control study (495 cases and 974 controls). Comparators were all residents of Ontario (randomly selected).	**Mining (at least 6 months)**	**Non-seminomas : OR = 12.39 (IC95% = 2.22-69.27)**
		Bakers et meat related work (at least 6 months)	**Non-seminomas : OR = 3.2 (IC95% = 1.39-7.35)**
		Metal products (at least 6 months)	Seminomas : OR = 0.49 (IC95% = 0.22-1.09)
26) Occupation and the Occurrence of Testicular Cancer. Stephen K. Van Den Eeden. 1991.	Case-control study (323 cases and 658 controls). Comparator was the US general population.	Metalmaking worker (at least 6 months)	For longest-worked occupation RR = 0.5 (IC95% = 0.1-4.9) For ever occupation : RR = 1.6 (IC95% = 0.3-7.9)
		Precision metal worker (at least 6 months)	For longest-worked occupation RR = 1 (IC95% = 0.3-3.6) For ever occupation : RR = 1.3 (IC95% = 1.5-3.9)
		Metalworking machine operator (at least 6 months)	For longest-worked occupation RR= 3.4 (IC95% = 0.4-29.2) For ever occupation : RR = 1.7 (IC95% = 0.3-10.9)
		Welder, cutter (at least 6 months)	For longest-worked occupation RR = 0.8 (IC95% = 0.2-3.0) For ever occupation : RR = 0.6 (IC95% = 0.2-1.8)
		Industry of mining and extracting (at least 6 months)	For longest-worked occupation 0 case For ever-worked : RR = 0.4 (IC95% = 0-3.2)
		Industry of metal product manufacturing (at least 6 months)	For longest-worked occupation RR = 1.4 (IC95% = 0.6-3.7) **For ever occupation : RR = 2.0 (IC95% = 1.0- 3.8)**
27) Occupational exposure to extreme temperature and risk of testicular cancer. Zhang ZF. 1995.	Case-control study (250 cases and 250 controls). Comparators were randomly selected from the neighborhood of each case.	**Only high temperatures at work (>80°F or >26.6°C)**	**OR = 2.15 (IC95% = 1.32-3.5)**
		High temperatures at work (>80°F or >26.6°C) > 10 years	**OR = 2.03 (IC95% = 1.11-3.72)**
		Bathing instead of showering	**OR = 2.93 (IC95% = 1.47-5.82)**

28) Social, behavioural and medical factors in the aetiology of testicular cancer: Results from the UK study. D. Forman. 1994.	Case-control study (794 cases and 794 matched controls). Comparators were randomly selected from the list of the general practitioner.	Underpants (usually worn)	Test for trend = 4.74 (p = 0.094) with "Y front underpants" as reference ; "boxers" RR = 1.02 (IC95% = 0.52-2.01)
		Tight fitting underpants worn	Test for trend = 0.55 (p = 0.46) with "never" as reference
		Material of underpants worn	**Test for trend = 7.64 (p = 0.022)** with "cotton" as reference ; **"nylon" RR = 1.81 (IC95% = 1.04-3.14)** ; "either" RR = 1.25 (IC95% = 1.01-1.55)
		Temperature of bath water	Test for trend = 4.80 (p = 0.31) with "always tepid" as reference
		Percentage of life in centrally heated accommodation	Test for trend = 0.82 (p = 0.37) with "none" as reference
29) Testicular cancer risk in relation to use of disposable nappies. H Møller. 2002	Case control study (296 cases and 287 controls). Comparator was the general Dannish population.	Use of disposable nappies during the 1946-1970 period	RR = 0.8 (IC95% = 0.3-2.0)
30) Testicular germ cell tumour risk by occupation and industry: a French case-control study. Margot Guth. 2023.	Case-control study (454 cases referred to CECOS center and 670 controls). Comparator was healthy fertile men who were sperm donors and partners of women consulting for fertility disorders (group A), and partners of women treated for a pathological pregnancy in specialized maternity clinics (group B)	Welders and flame-cutters	OR = 1.4 (IC95% = 0.59-3.29)
		Metalworking industry	OR = 0.84 (IC95% = 0.44-1.61

Only significant results are summarized following extraction data from 12 studies, and ranked by heat exposures (*Table4*).

Table 4: Only significant results

Type of heat exposure	Heat exposure	Title of the article. Main author. Publication year.	Study type. Comparator(s).	Main outcome results (testicular cancer)
Clothing increasing testicular temperatures	Material of underpants worn	28) Social, behavioural and medical factors in the aetiology of testicular cancer: Results from the UK study. D. Forman. 1994.	Case-control study (794 cases and 794 matched controls). Comparators were randomly selected from the list of the general practitioner.	Test for trend = 7.64 (p = 0.022) with "cotton" as reference "nylon" RR = 1.81 (IC95% = 1.04-3.14)
Prolonged sitting position	Fighter aviators (pilots and backseat aircrew)	2) Cancer Incidence and Mortality Among Fighter Aviators in the United States Air Force. Niklas Hammar. 2002.	Cohort (34 976 fighter aviators). Comparator was the general US population.	RR = 0.38 (IC95% = 0.27-0.51)
	Fighter aviators (pilots and backseat aircrew)	2) Cancer Incidence and Mortality Among Fighter Aviators in the United States Air Force. Niklas Hammar. 2002.	Cohort (34 976 fighter aviators). Comparators were the other officers.	RR = 1.30 (IC95% = 1.01-1.93)
	Pilots (including pilot trainees)	24) Military occupation and testicular germ cell tumour risk among US Air Force servicemen. Christina Denic-Roberts. 2023.	Nested case–control study (530 cases and 530 matched controls of active duty USAF servicemen). Comparator was the USAF servicemen who had no history of any malignancies except for non-melanoma skin cancer.	OR=1.78 (IC95% = 1.06–3.01)
	Drivers	17) Time trends and occupational variation in the incidence of testicular cancer in the Nordic countries. Outi Ylönen. 2018.	Epidemiological study (26 million inhabitants of the five Nordic countries : Denmark, Finland, Iceland, Norway, Sweden). Comparator was the general population of the Nordic countries.	Seminoma : SIR = 0.88 (IC95% = 0.77–1.0)
	Drivers (of cars, taxis, vans, buses, motorcycles, trams, and light and heavy trucks)	18) Work-related cancer in the Nordic countries. Andersen A. 1999.	Cohort (10 millions included). Comparator was the general population of the Nordic countries.	SIR = 0.8 (IC95% = 0.69-0.92)
Testicular contact to external hot sources	Hot tub or sauna use (for 0 month, 2-6 months, and >6 months)	21) Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Margaret R KARAGAS. 1989.	Case-control study (323 cases, 675 contrôles). Comparator was the white males between 20 and 69 years of age randomly selected in the same area.	RR (1 month) = 0.5 (IC95% = 0.4-0.7) RR (2-6 months) = 0.5 (IC95% = 0.3-0.8) RR (> 6 months) = 0.5 (IC95% = 0.3-0.8)
	Bathing (VS showering)	27) Occupational exposure to extreme temperature and risk of testicular cancer. Zhang ZF. 1995.	Case-control study (250 cases and 250 controls). Comparators were randomly selected from the neighborhood of each case.	OR = 2.93 (IC95% = 1.47-5.82)
Occupational heat exposures	Metal annealer, temperer main occupation (exposure time not cited)	9) Incidence of Testicular Cancer and Occupation among Swedish Men Gainfully Employed in 1970. Marina Pollán. 2001.	Historical cohort (31 668 842 person-years of Swedish men who were gainfully employed at the time of 1960 and 1970 census). Comparator was the total cohort.	Seminomas : RR = 5.85 (IC95% = 1.88-18.20)
	Metal annealer, temperer at 1960 and 1970 census (> 10 years of work)	9) Incidence of Testicular Cancer and Occupation among Swedish Men Gainfully Employed in 1970. Marina Pollán. 2001.	Historical cohort (31 668 842 person-years of Swedish men who were gainfully employed at the time of 1960 and 1970 census). Comparator was the total cohort.	Seminomas : RR = 21.89 (IC95% =7.04-68.06)

	Construction smith at 1960 and 1970 census (more than > 10 years of work)	9) Incidence of Testicular Cancer and Occupation among Swedish Men Gainfully Employed in 1970. Marina Pollán. 2001.	Historical cohort (31 668 842 person-years of Swedish men who were gainfully employed at the time of 1960 and 1970 census). Comparator was the total cohort.	Seminomas : RR = 3.29 (IC95% = 1.06-10.22)
	Furnace workers (at least 6 months)	15) Study of cancer incidence among 8530 male workers in eight Norwegian plants producing ferrosilicon and silicon metal. Ånund Hobbesland. 1999.	Historical cohort study (8 530 metal workers, 193 930 person-years). Comparator was the general Norwegian population.	SIR = 2.3 (IC95% = 1.05-4.37)
	Smelter and metal foundry workers	18) Work-related cancer in the Nordic countries. Andersen A. 1999.	Cohort (10 millions included). Comparator was the general population of the Nordic countries.	SIR = 0.78 (IC95% = 0.6-1.0)
	Welders and flame-cutters	19) Case–Control Study of Male Germ Cell Tumors Nested in a Cohort of Car-Manufacturing Workers: Findings From the Occupational History. Ingo Langner. 2010.	Case-control study nested in a cohort of car-manufacturing workers (205 cases, 1105 controls). Comparator was the workers in the same factories as the cases for at least 6 months.	OR = 1.57 (IC95% = 1.06-2.34)
	Industry of metal product manufacturing (ever worked, at least 6 months)	26) Occupation and the Occurrence of Testicular Cancer. Stephen K. Van Den Eeden. 1991.	Case-control study (323 cases and 658 controls). Comparator was the US general population.	RR = 2.0 (IC95% = 1.0- 3.8)
	Only high temperatures (>80°F or >26.6°C) at work	27) Occupational exposure to extreme temperature and risk of testicular cancer. Zhang ZF. 1995.	Case-control study (250 cases and 250 controls). Comparators were randomly selected from the neighborhood of each case.	OR = 2.15 (IC95% = 1.32-3.5)
	High temperatures at work (>80°F ou >26.6°C) > 10 years	27) Occupational exposure to extreme temperature and risk of testicular cancer. Zhang ZF. 1995.	Case-control study (250 cases and 250 controls). Comparators were randomly selected from the neighborhood of each case.	OR = 2.03 (IC95% = 1.11-3.72)
	Mining (at least 6 months)	25) Occupation and risk of germ cell testicular cancer by histologic type in Ontario. Knight. 1995.	Case-control study (495 cases and 974 controls). Comparators were all residents of Ontario (randomly selected).	Non-seminomas : OR = 12.39 (IC95% = 2.22-69.27)
	Bakers et meat related work (at least 6 months)	25) Occupation and risk of germ cell testicular cancer by histologic type in Ontario. Knight. 1995.	Case-control study (495 cases and 974 controls). Comparators were all residents of Ontario (randomly selected).	Non-seminomas : OR = 3.2 (IC95% = 1.39-7.35)

Narrative analysis (qualitative analysis) by study type: only significant results

2) Cancer Incidence and Mortality Among Fighter Aviators in the United States Air Force. Niklas Hammar. 2002.

This retrospective cohort study followed US Air Force officers who served between 1970 and 2004. The study analyzed incidence and mortality rates of testicular cancer. The fighter aviator population (including pilots and rear aircrew) was compared both to the overall US population and to the other non-air force officers. Results for US Air Force fighter pilots compared with the overall US population showed a significant negative association with testicular cancer risk (RR = 0.38 with IC95% = 0.27-0.51), with 43 observed cases. When compared to other officers (matched on sex, age group at entry into active service and age group at incidence censoring), results showed a significant positive association with testicular cancer (RR = 1.30 with IC95% = 1.01-1.93), with 43 cases.

9) Incidence of Testicular Cancer and Occupation among Swedish Men Gainfully Employed in 1970. Marina Pollán. 2001.

This historical cohort studied the incidence of testicular cancer by occupation in all Swedish men aged > 24 years who were gainfully employed at the time of the 1960 and 1970 censuses. In the following results, RR1 is the relative risk of occupations in the cohort that participated in one of the two censuses (= at some point), relative to the total population of the cohort. RR2 is a more precise definition since it is calculated for occupations that are retained in both censuses (= working time >10 years). Of the total number of 31,668,842 person-years included in the cohort, 784 seminomas and 405 non-seminomas (95% of which were teratomas) were recorded. Metal annealers and temperers are exposed to heat because annealing of a material is a process corresponding to a heating cycle that consists of a gradual rise in temperature followed by a controlled cooling. Those occupations were significantly positively associated with seminomas both at a given time (RR1 = 5.85 with IC95% = 1.88-18.2) and for a prolonged duration work > 10 years (RR2 = 21.89 with IC95% = 7.04-68.06), for 3 observed cases. Construction smiths workers are also exposed to heat because it requires processing hot metals using different tools and performs forging work (heating, welding, shaping, processing, manufacturing mechanical parts for machines, etc). This occupation was significantly positively associated with seminomas only for a prolonged duration work > 10 years (RR2 = 3.29 with IC95% = 1.06-10.22), for 3 observed cases. Concrete and construction workers were significantly positively associated with non-seminomas both at a given time (RR1 = 1.71 with IC = 1.01-2.92, for 14 cases observed) and for a prolonged duration work > 10 years (RR2 = 3.80 with CI = 1.70-8.51), for 6 observed cases.

This study clearly separates the analysis of seminomatous and nonseminomatous subtypes of testicular cancer, that highlights the need to study these tumors separately. Until now, most of the studies combined the two types of tumors allowing certainly an increase in statistical power, but which could be responsible for the differences and contradictions found in the literature. We can also note that cancer incidence appears to be increased both at a given time and for more than 10 years of work, but with a time-related strength of association.

15) Study of cancer incidence among 8530 male workers in eight Norwegian plants producing ferrosilicon and silicon metal. Ånund Hobbesland. 1999.

This historical cohort studied the association between work in Norwegian factories producing metal (ferrosilicon and silicon) and the incidence of various cancers including testicular cancer. Among the 2534 furnace workers compared to the general Norwegian population, a significant increase in the standardized incidence ratio of testicular cancer was found (SIR = 2.3 with CI = 1.05-4.37), with 9 observed cases (of which 4 were seminomas, 1 was embryonic carcinoma, 2 were teratomas and 2 were unspecified tumors). Results also found a significant increase in the standardized incidence ratio for furnace workers who had started their occupation “less than 5 years ago” (SIR = 5.88 with CI = 1.91-13.7), with 5 observed cases, whereas no association were found for a work duration of “5-9 years”, “10-19 years” and > 20 years”.

This study reveals a significantly increased incidence of testicular cancer among metal workers in blast furnaces, that appears to be mainly during the first 5 years of work. These results are surprising and would indicate a rather rapid appearance of testicular cancer after exposure to metal crafts in blast furnaces. Moreover, it is interesting to note that only one of the nine cases of testicular cancer died of the disease between 1962 and 1990. Thus, cancer mortality studies may miss an increased testicular cancer incidence.

17) Time trends and occupational variation in the incidence of testicular cancer in the Nordic countries. Outi Ylönen. 2018.

This epidemiological study was conducted as a cohort and investigated 45 years of testicular cancer incidence by occupation in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden), using national cancer registries. Cancer database covers 15 million people aged 30–64 years, and more than 2.8 million incident cancers diagnosed before 2005. For drivers, results showed a significant decrease in the standardized incidence of seminoma (SIR = 0.88 with CI = 0.77–1.00).

18) Work-related cancer in the Nordic countries. Andersen A. 1999.

This epidemiological study was conducted as a cohort and investigated 45 years of testicular cancer incidence by occupation in the Nordic countries (Denmark, Finland, Norway and Sweden), using national cancer registries. Cancer database covers 10 million people aged 25-64 years, and 1 million incident cancers diagnosed. Drivers (of cars, taxis, vans, buses, motorcycles, trams and light and heavy trucks) were associated with a significant decrease in the standardized testicular cancer incidence (SIR = 0.8 with CI = 0.69-0.92) with 199 cases/259 696. Foundry and metal foundry workers (including ore and metal furnace operators, metal foundry operators, smelters and rolling mills, metal heat treatment plant operators, metal drawers and extruders) ensure the operation and control of smelting furnaces, refining, converting or reheating metal. These occupations were associated with a significant decrease in the testicular cancer incidence (SIR = 0.78 with CI = 0.6-1.0) with 63 cases/77 288.

19) Case–Control Study of Male Germ Cell Tumors Nested in a Cohort of Car-Manufacturing Workers: Findings From the Occupational History. Ingo Langner. 2010.

This case-control study of testicular cancer (205 cases and 1 105 controls) was conducted, based on data collected between 1989 and 2004 from a cohort of 202 000 auto construction workers in Germany. The odds ratio (OR) of several occupations and industries were studied with an adjustment on cryptorchidism. Results for “welders and flame-cutters” showed a significant positive association with testicular cancer (OR2 = 1.57 with IC95% = 1.06-2.34). These occupations came from a larger group “plumbers, welders, sheet and structural metal workers” which show no significant association with testicular cancer (OR = 1.4 with IC95% = 0.99-1.95).

21) Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Margaret R KARAGAS. 1989.

This American case-control study investigated the potential role of heat in 323 testicular cancer cases and 675 controls between 20 and 69 years of age randomly selected in the same geographic area. Spa and sauna exposures (for 0, 2-6, and >6 months) were significantly negatively associated with testicular cancer (respectively RR “1 month” = 0.5 with IC95% = 0.4-0.7, RR “2-6 months” = 0.5 with IC95% = 0.3-0.8, RR “> 6 months” = 0.5 with IC95% = 0.3-0.8), with respectively 106, 17, 16 observed cases. Those results were significantly objectified rather for seminomas than for non-seminomas (RR seminomas “> 6 months” = 0.3 with IC95% = 0.1-0.7, VS RR non-seminomas “> 6 months” = 0.7 with IC95% = 0.3-1.4).

24) Military occupation and testicular germ cell tumour risk among US Air Force servicemen. Christina Denic-Roberts. 2023.

This case-control study of US Air Force Servicemen (530 cases and 530 matched controls) studied the distribution of testicular cancers in several occupations among US Air Force members. It comes from another case-control study about serum per- and polyfluoroalkyl substances (PFAS) and testicular cancer risk among the same population. Occupational exposures were recorded twice: at the time of serum collection (time 1) which averaged 2.4 years after military accession, and at the time of diagnosis of testicular cancer (time 2) which averaged 8.2 years after military accession. In addition, a stratified analysis by testicular subtype (seminomas and non-seminomas) was performed in this study. The results at the time of diagnosis (time 2) for all pilots (including aircraft pilots, fighter pilots, and trainee pilots) were significantly positively associated with testicular cancer (OR = 1.78 with IC95% = 1.06-3.01), with 46 observed cases. In addition, the analysis at both data collection times (times 1 and 2, on average 6 years difference) in pilots also found a significant increase in the risk of testicular cancer (OR = 1.87 with IC95% = 1.06-3.27), which strengthens the association.

25) Occupation and risk of germ cell testicular cancer by histologic type in Ontario. Knight JA. 1995.

This case-control study of Ontario residents (495 cases and 974 controls) studied the distribution of testicular cancers in several occupations carried out at least for 6 months. The results for “mining'' showed a significant positive association with non-seminomas type of cancer (OR = 12.39 with IC95% = 2.22-69.27). For “bakers and meat related work”, there was also a significant positive association with non-seminomas type of cancer (OR = 3.2 with IC95% = 1.39-7.35).

26) Occupation and the Occurrence of Testicular Cancer. Stephen K. Van Den Eeden. 1991.

This case-control study (323 cases and 658 matched controls) investigated the association between several occupations and the risk of testicular cancer in western Washington. For each type of occupation, two analyses were carried out : RR1 for the occupational type worked the longest, equivalent to the main job during lifetime, and RR2 for the occupational type worked

for at least 6 months. For the “metal manufacturing industry”, there was a significantly positive association with testicular cancer for at least 6 months’ work (RR2 = 2.0 with CI = 1.0-3.8) with 5.3% of cases and 2.7% of controls. From this industry, the “precision metal worker” occupation was significantly positively associated with testicular cancer for at least 6 months’ work (RR2 = 1.3 with CI = 1.5-3.9), with 1.9% of cases and 1.5% of controls.

27) Occupational exposure to extreme temperature and risk of testicular cancer. Zhang ZF. 1995.

This case control study (250 cases and 250 controls from the general population matched by age and residence), investigated the relationship between testicular cancer and occupational exposures to high temperature (> 80°F = 26.6°C), low temperature (< 60°F = 15.5°C), and extreme temperature (together high > 80°F or low < 60°F). Temperature exposures were assessed by questionnaires. The crude odds ratios of testicular cancer were significantly positively associated for workers exposed to only high temperature at work (crude OR = 2.15 with IC95% = 1.32-3.5, with 59 cases and 42 controls). Then with a multiple logistic regression model, the relationship with years of exposure showed a significantly positive association for two types of exposure : for > 10 years of exposure to high temperature (OR = 2.03 with IC95% = 1.11-3.72), and for bathing instead of showering (OR = 2.93 with IC95% = 1.47-5.82).

Another finding from the study was that exposure to low temperatures at work was also significantly associated with testicular cancer risk (adjusted OR = 1.7 with IC95% = 1.04-2.78).

28) Social, behavioural and medical factors in the aetiology of testicular cancer: Results from the UK study. Forman D. 1994.

This case-control study (794 cases and 794 matched controls) was carried out on the general population from nine regions in England and Wales and investigated risk factors for testicular cancer. For the “material of underpants worn” parameter, results showed a significant positive trend (test for trend = 7.64 with p = 0.022) with “cotton” as reference. The subgroup analysis for “nylon type” and “either type” showed an increased positive association with testicular cancer (respectively RR = 1.81 with IC95% = 1.04-3.14, and RR = 1.25 with IC95% = 1.01-1.55).

Bias assessments:

As articles included for analysis were only case-control and non-randomized cohort studies, we thus used The NewCastle Ottawa (NCO) assessment tool proposed by Cochrane for alternative to the ROBINS-1 tool for those types of studies.

- For non-randomized cohorts (*Table5*) : two articles had a score of 5/9, one had a score of 6/9 than 7/9, and sixteen had a score of 7/9 or higher.
- For case-control studies (*Table6*) : two had a score lower of 5/9, and ten had a score of 7/9 or higher.

It shows a good overall quality of the selected studies with a total of 26 studies with a score of 7/9 or higher.

Table 5: Bias assessment of non-randomized cohorts

Articles	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	TOTAL
1		★	★		★★	★	★	★	7
2		★	★		★★	★	★	★	7
3		★	★		★★	★	★	★	7
4		★	★		★★	★	★	★	7
5		★	★		★★	★	★	★	7
6		★	★		★★	★	★	★	7
7		★	★		★★	★	★	★	7
8		★	★		★★	★	★	★	7
9	★	★	★			★	★	★	6
10		★	★			★	★	★	5
11		★	★			★	★	★	5
12		★	★		★★	★	★	★	7
13		★	★		★★	★	★	★	7
14	★	★	★		★★	★	★	★	8
15		★	★		★★	★	★	★	7
16	★	★	★		★★	★	★	★	8
17	★	★	★		★★	★	★	★	8
18	★	★	★		★★	★	★	★	8

Table 6: Bias assessment of case-control studies

Articles	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure (bind status)	Same method of ascertainment for cases and controls	Non-Response rate (maximum 5% difference)	TOTAL
19	★	★	★	★			★		5
20	★	★	★	★	★★	★	★	★	9
21	★	★	★	★	★★		★	★	8
22	★	★	★	★			★		5
23	★	★	★	★		★	★	★	7
24	★	★	★	★		★	★	★	7
25	★	★	★	★	★★	★	★	★	7
26	★	★	★	★	★★		★		7
27	★	★	★	★	★★		★		7
28	★	★	★	★			★		7
29	★	★	★	★	★★		★		7
30	★	★	★	★		★	★	★	7

Meta-analysis (quantitative analysis) of significant results:

Each meta-analysis took into account: at least 3 significant results, for same type of results, from cohort studies, according to the inclusion and exclusion criteria (compared only with the general population), and with studies that have a high quality of bias assessment (studies that have a score 7/9 or higher). 4 studies were selected for the realization of two meta-analyses.

1) Meta-analysis from non-randomized cohorts with SIR (Standardized Incidence Ratio) as measures of effects (*Figure2,3,4*)*:*

A total of 2 studies (*15, 18*) and k=3 heat exposures were included in the analysis (furnace workers, foundry workers, drivers). The observed log odds ratios ranged from -0.2487 to 8.4788, with most estimates being negative (67%). The estimated average log odds ratio based on the random-effects model was \hat{\mu} = 2.6420 (95% CI: -3.0250 to 8.3090). Therefore, the average outcome did not differ significantly from zero (z = 0.9138, p = 0.3608). According to the Q-test, the true outcomes appear to be heterogeneous (Q(2) = 207.5725, p < 0.0001, tau2 = 24.9535, I2 = 99.9193%). A 95% prediction interval for the true outcomes is given by -8.6705 to 13.9545. The regression test indicated funnel plot asymmetry (p < 0.0001) but not the rank correlation test (p = 0.3333).

Figure 2: Forest plot for non-randomized cohorts with SIR as measure of effects

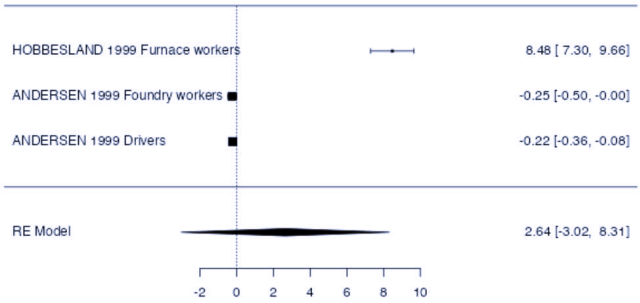


Figure 3: Funnel plot for non-randomized cohorts with SIR as measure of effects

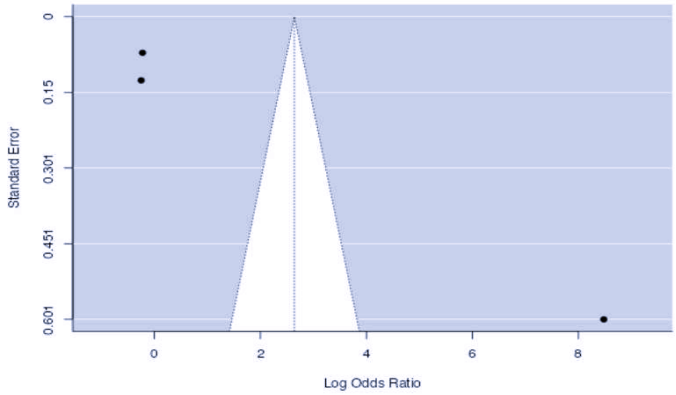


Figure 4: Publication bias for non-randomized cohorts with SIR as measure of effects

Fail-Safe N Analysis (File Drawer Analysis)

Fail-safe N	p
28.000	<.001

Note. Fail-safe N Calculation Using the Rosenthal Approach

Rank Correlation Test for Funnel Plot Asymmetry

Kendall's Tau	p
1.000	0.333

Regression Test for Funnel Plot Asymmetry

Z	p
8.426	<.001

2) Meta-analysis from case-control studies with OR (Odds ratios) as measures of effects (Figure5,6,7):

A total 2 studies (*25, 27*) and k=3 heat exposures were included in the analysis (mining, bathing instead of showering, only high exposure at work). The observed log odds ratios ranged from 0.4251 to 1.9418, with the majority of estimates being positive (100%). The estimated average log odds ratio based on the random-effects model was \hat{\mu} = 0.8912 (95% CI: 0.1683 to 1.6141). Therefore, the average outcome differed significantly from zero (z = 2.4164, p = 0.0157). The Q-test for heterogeneity was not significant, but some heterogeneity may still be present in the true outcomes (Q(2) = 4.7194, p = 0.0945, tau2 = 0.2271, I2 = 57.7284%). A 95% prediction interval for the true outcomes is given by -0.2898 to 2.0723. The regression test indicated funnel plot asymmetry (p = 0.0329) but not the rank correlation test (p = 0.3333).

Figure 5: Forest plot for case-control studies with OR as measure of effects

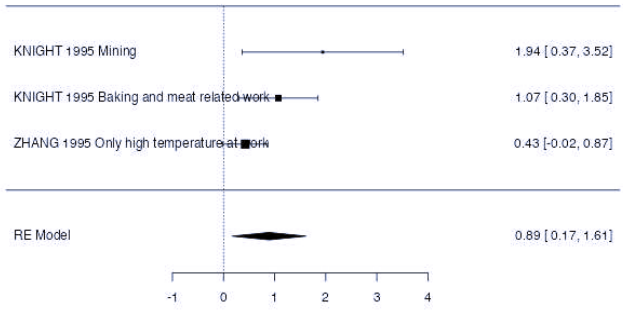


Figure 6: Funnel plot for case-control studies with OR as measure of effects

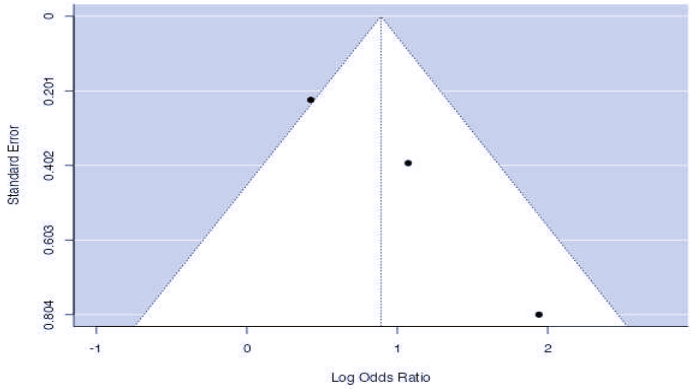


Figure 7: Publication bias for case-control studies with OR as measure of effects

Fail-Safe N Analysis (File Drawer Analysis)

Fail-safe N	p
16.000	<.001

Note. Fail-safe N Calculation Using the Rosenthal Approach

Rank Correlation Test for Funnel Plot Asymmetry

Kendall's Tau	p
1.000	0.333

Regression Test for Funnel Plot Asymmetry

Z	p
2.133	0.033

D. Discussion

Main results:

For clothing increasing testicular temperatures, we found no significant results for an association with testicular cancer. For prolonged sitting position, drivers showed a significant decrease in the standardized incidence of seminoma in two studies, and pilots showed significant contradictory results. For testicular contact to external hot sources, spa and sauna exposures showed significant negative associations with testicular cancer for all time exposures (0, 2-6, and >6 months), whereas bathing instead of showering showed a significant positive association with testicular cancer. For occupational heat exposures, bakers and metal industry workers showed a significant positive association with testicular cancer. Overall, this study states a possible link between testicular cancer and only high external heat exposures (represented by occupational heat exposures particularly in the metal industry).

Clothing increasing testicular temperatures:

For tight clothing, soiled diapers covered in plastic, or professional cyclists, we found no significant results for an association with testicular cancer. Though, we found that the "nylon" type of underwear was at greater risk of testicular cancer.(28) In fact, nylon is a synthetic polyamide type of plastic tissue. A study(107) investigating the evaporation capacities of three different tissues found that nylon tissue was the tissue delaying most the return to heating level after being wet. Those findings do not support our first hypothesis that testicular cancer is associated with an increased external heat. Testicular cancer may rather be associated with a tissue that prevents sweat from evaporating. It could be interesting to investigate the role of some work uniforms that prevent sweat from evaporating, such as in military workers, firefighter workers, police workers, or construction workers. Among firefighters, it is interesting to note that three recent meta-analyses(108)(109)(110) have attested a probable increase in testicular cancer among firefighters, although no exposure factor has formally been found.

Prolonged sitting position:

For drivers, there was a significant decrease in the standardized incidence of seminoma in two studies.(17, 18) Those results are surprising considering our initial hypothesis. The main limitation of those studies is the absence of information on exposure durations of driving and a possible classification bias since workers can change jobs during their lives. Another bias could be the numerous statistical analyses carried out (global population of about 26 millions inhabitants) that could have generated randomly significant results when they were not in reality (alpha risk). For pilots(2, 24) the association was both positive when compared to other officers (internal comparison group), and negative when compared to the general population (external comparison group), demonstrating the importance of the comparators used in the statistical analysis. The use of an internal comparison group helps to take confounding factors into account, but it also reduces the external validity of a study. In fact, the military population is highly selected in terms of educational, physical, and medical standards that could induce a powerful "healthy worker effect"(46)(99)(111) reducing the overall testicular cancer risk. Another possible confounding between the link of occupational pilots and testicular cancer is the exposure to glycol esters in aviation fuel(99). For people in a wheelchair, we found no significant results. Moreover, most of the case reports in this study population showed a testicular cancer metastasis that caused paraplegia and not the opposite(112)(113). Thus, prolonged sitting positions seem to be rather negatively associated with testicular cancer, which does not support our first hypothesis. Questions about some results remain to be answered, but the choice of controls in studies could be a key factor.

Testicular contact to external hot sources:

For the use of a laptop, no study was found investigating an association with testicular cancer. For spa and sauna exposures, significant negative associations with testicular cancer were found for all time exposures (0, 2-6, and >6 months)(21), and those results seemed to be

rather for seminomas than for non-seminomas. For bathing instead of showering results showed a significant positive association with testicular cancer.(27) The main limitation of those studies was that results came from questionnaires about lifestyle habits inducing a lack of either an accurate exposure time, or an accurate temperature cited. Thus, those contradictory results did not support our first hypothesis. Further research is needed with accurate measures.

Occupational heat exposures:

For oven operators, no result was found for an association with testicular cancer. For submariners, only one result was found but no significant.(23) For bakers, a significant positive association with non-seminomas was found(25), even if it was an exposure including "meat related work". For underground miners, results showed a significant positive association with non-seminomas.(25) For working in a metal industry, results showed a significant positive association with testicular cancer.(26) If we looked at specific metal industry occupations : we had significant positive associations for metal annealers and temperers(9), construction smith workers(9) and welders and flame-cutters(19), and we had contradictory results for furnace workers.(15, 18) Thereby, except for two negative results, most of the studies about occupational heat exposures showed a significant positive association with testicular cancer. Those results appeared to support our first hypothesis that external heat could be at risk of testicular cancer. To go further, occupational heat exposures in the metal industry are at higher levels of heat than the other types of heat studied here (especially clothing increasing testicular temperatures and prolonged sitting positions), which may indicate a possible link between external heat exposures to only high temperatures (represented by the metal industry) and testicular cancer.

Meta-analyses:

The first meta-analysis from standard incidence ratios showed a non-significant positive effect of heat exposures on the incidence of testicular cancer. The second meta-analysis from odds ratios showed a significant positive effect of heat exposures on the association with testicular cancer. However for the two meta-analyses, although the average outcome is estimated to be positive, in some studies the true outcome may in fact be negative. An examination of the studentized residuals revealed that none of the studies had a value larger than ± 2.3940 and hence there was no indication of outliers in the context of this model. According to the Cook's distances, none of the studies could be considered to be overly influential. In the end, the heterogeneity was too large to come to any conclusions. These discordant results could be explained by:

- *Statistical limitations:* the standard Incidence Ratio (SIR)(114) is an estimate of the number of cancer cases in a given population compared to what might be "expected" based on a comparison with the cancer experience in a larger population. Standardizing is a way to adjust a rate by considering factors about a population such as age, sex, race, or ethnicity. Therefore, as a statistical estimate, the interpretation of the SIR is not straightforward. SIRs that are

greater than 1.0 (or 100) should be explored further but sometimes a SIR greater than 1.0 (or 100) may be due to random chance. The results from the SIR meta-analysis should be interpreted with caution, especially with non-significant results like in our study.
Odds Ratios are used to determine if a particular exposure is a risk factor for a particular outcome, and to compare the magnitude of various risk factors for that outcome. The odds ratio is a good estimate of association in a population for which the prevalence of the outcome is less than 10% (such as the prevalence of testicular cancer which is about 1% of the population). But different odds ratios from a same study cannot be compared when different variables are used, and the odds ratios from one study cannot be compared with the odds ratio from another study because the scaling factors are different. Thus, an association evaluated by different studies cannot be synthesised in a meta-analysis without error(115).
- *A true high heat exposure effect:* the results from the meta-analyses are in accordance with the narrative conclusion. In fact, all together, the four types of heat exposure studied seemed to be not at higher risk of testicular cancer, but when only high heat exposures are studied (like working in metal industries or in bakeries), there may be a higher risk of testicular cancer, that could be explored in further research.

Subtypes of testicular cancer:
Seminomas seemed to be positively associated with metal annealer and temperer(*9*), construction smith workers(*9*), and negatively associated with drivers(*17*), spa and sauna exposures.(*21*) Non-seminomas seemed to be positively associated mining(*25*), bakers and meat related workers.(*25*) Therefore, etiologic risk factors for seminomas may be different from non-seminomas, as different results were found when studying those subtypes separately.

Limits and advantages of the study:
- *Limits:* firstly, one of the major limits of this study is the lack of temperature measurement of the different heat exposures. To limit this measurement bias, before starting the study we made a non-systematic review of what kind of heat exposure could have a real impact on either sperm parameters, or a significant impact on body temperature (references in the introductory part). Secondly, the minimum threshold heat exposure was 3 months in our exclusion criteria, corresponding to the time needed for a germ cell to mature and become a sperm cell capable of fertilizing an egg. This threshold is appropriate for fertility disorders studies but could be not appropriate for the occurrence of testicular cancer. In most of our studies, exposure time was “at least 6 months”, “main occupation” or “usually worn” so it may represent enough exposure time, but as we don’t really know the heat exposure time required for the occurrence of testicular cancer, this parameter could change in further studies. Third, the heterogeneity of meta-analyses was too large to come to any conclusions.
- *Advantages:* firstly, we made this systematic review in accordance with the PRISMA guidelines, with a double-blind selection strategy. Secondly, to increase external validity of the study, we chose an external comparator which was only healthy men from the general population. Though, for the narrative analysis, it seemed important to show also internal

comparators in some studies, because results can highly differ depending on the comparator chosen. As an example, in one of the studies about pilot occupations(*2*), for the same results, there was a significant negative association with the “general population” comparator, and a significant positive association with the “other officers” comparator. Third, bias assessment according to the NOS tool showed a good overall quality of the selected studies (26 studies with a score of 7/9 or higher). Fourth, this study was the first meta-analysis on the subject and could be useful for the development of male thermal contraception methods.

Conclusion and perspectives:

Our study cannot conclude that there is a link between external heat exposures and testicular cancer with the two meta-analyses carried out, because of the heterogeneity of results. However, with the narrative analysis, we can hypothesise that there may be a link between external heat exposures to only high temperatures (represented by the metal industry) and testicular cancer. There must be a threshold for which heat exposures could be at higher risk of testicular cancer. That “heat threshold” remains to be explored and should integrate parameters such as an exposure duration and a wet index (because wetness is known to fluctuate heat perception).(116). Regarding male thermal contraception, it seems that the slight increase of testicular temperature induced by the device should not be at higher risk of testicular cancer. But more appropriate studies with male thermal contraception device are needed to state a conclusion on this subject.

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Ethic, funding, competing interests:

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V. APPENDIX

Annex 1: Search queries

Database	Search queries
PUBMED (17/09/23)	((testicular neoplasm[Majr]) OR (testicular cancer[Title/Abstract]) OR (testicular malignancy[Title/Abstract]) OR (scrotal cancer*[Title/Abstract]) OR (scrotal neoplasm*[Title/Abstract]) OR (cancer of the testis[Title/Abstract]) OR (testis cancer[Title/Abstract])) AND ((extreme heat[Title/Abstract]) OR (temperature*[Title/Abstract]) OR (hot[Title/Abstract]) OR (heat[Title/Abstract]) OR (heating[Title/Abstract]) OR (hyperthermia[Title/Abstract]) OR (clothing[Majr]) OR (underclothes[Title/Abstract]) OR (underwear*[Title/Abstract]) OR (nappies[Title/Abstract]) OR (childbed[Title/Abstract]) OR (cyclist[Title/Abstract]) OR (sauna[Title/Abstract]) OR (baths[Title/Abstract]) OR (bathing[Title/Abstract]) OR (hammam[Title/Abstract]) OR (hot tub[Title/Abstract]) OR (laptop[Title/Abstract]) OR (sitting[Title]) OR (sedentary[Title]) OR (driver[Title/Abstract]) OR (pilots[Title/Abstract]) OR (paraplegia[Title/Abstract]) OR (paraplegic[Title/Abstract]) OR (tetraplegia[Title/Abstract]) OR (tetraplegic[Title/Abstract]) OR (wheelchair[Title/Abstract]) OR (outdoor work[Title/Abstract]) OR (foundry[Title/Abstract]) OR (steel industry[Title/Abstract]) OR (iron industry[Title/Abstract]) OR (welder[Title/Abstract]) OR (furnace[Title/Abstract]) OR (metallurgy[Title/Abstract]) OR (miner[Title/Abstract]) OR (ovens[Title/Abstract]) OR (baker[Title/Abstract]) OR (submariner[Title/Abstract])) NOT ((cryptorchid*[Title/Abstract]) OR (varicocele[Title/Abstract]) OR (inguinal hernia[Title/Abstract]) OR (hydrocele[Title/Abstract]) OR (inflammation[Title/Abstract]) OR (obesity[Title/Abstract]) OR (Toxic Actions[MeSH Terms]) OR (Genetic Phenomena[MeSH Terms]) OR (skin neoplasms[MeSH Terms]) OR (therapy[Title]) OR (therapeutic[Title]) OR (treatment[Title]))
EMBASE (17/09/23)	('testicular neoplasm'/de OR 'testicular cancer':ab,ti OR 'testicular malignancy':ab,ti OR 'scrotal cancer':ab,ti OR 'scrotal neoplasm':ab,ti OR 'cancer of the testis':ab,ti OR 'testis cancer':ab,ti) AND ('extreme heat':ab,ti OR 'temperature':ab,ti OR 'hot':ab,ti OR 'heat':ab,ti OR 'hypertherm':ab,ti OR 'clothing'/de OR 'trousers':ab,ti OR 'pants':ab,ti OR 'underwear':ab,ti OR 'boxer':ab,ti OR 'nappies':ab,ti OR 'childbed':ab,ti OR 'cyclist':ab,ti OR 'sauna':ab,ti OR 'baths':ab,ti OR 'hammam':ab,ti OR 'hot tub':ab,ti OR 'laptop':ab,ti OR 'sitting':ab,ti OR 'sedentary':ab,ti OR 'driver':ab,ti OR 'pilots':ab,ti OR 'paraplegia':ab,ti OR 'tetraplegia':ab,ti OR 'paraplegic':ab,ti OR 'tetraplegic':ab,ti OR 'outdoor work':ab,ti OR 'foundry':ab,ti OR 'furnace':ab,ti OR 'steel industry':ab,ti OR 'iron industry':ab,ti OR 'welder':ab,ti OR 'metallurgy':ab,ti OR 'baker':ab,ti OR 'oven':ab,ti OR 'miner':ab,ti OR 'submariner':ab,ti) NOT ('cryptorchid':ab,ti OR 'varicocoele' OR 'varicocele':ab,ti OR 'inguinal hernia':ab,ti OR 'hydrocele':ab,ti OR 'toxic actions'/de OR 'genetic phenomena'/de OR 'skin neoplasms'/de OR 'therapy':ti OR 'therapeutic':ti OR 'treatment':ti)
COCHRANE (17/09/23)	ID Search Hits #1 testicular neoplasm 137 #2 testicular cancer 654 #3 testicular malignancy 43 #4 scrotal cancer 42 #5 scrotal neoplasm 8 #6 cancer of the testis 382 #7 testis cancer 403 #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 907 #9 extreme heat 240 #10 temperature 27750 #11 hot 10759 #12 heat 10615 #13 heating 1838 #14 hyperthermia 2021 #15 clothing 1868 #16 cyclist* 1396 #17 nappies 38 #18 sauna 179 #19 baths 886 #20 bathing 1278 #21 hammam 26

	#22 hot tub 49 #23 laptop 717 #24 sitting 10637 #25 sedentary 10001 #26 driver 2780 #27 pilots 327 #28 paraplegia 800 #29 paraplegic 213 #30 tetraplegia 303 #31 tetraplegic 116 #32 wheelchair 1042 #33 outdoor work 276 #34 foundry 15 #35 steel industry 66 #36 iron industry 129 #37 welder* 24 #38 furnace* 53 #39 metallurgy 60 #40 miner 396 #41 oven* 159 #42 baker* 7092 #43 submariner 0 #44 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #28 OR #29 OR #30 OR #31 OR #32 #33 #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 75639 #45 #8 AND #44 40
Web of Science (17/09/23)	(TS=(testicular neoplasm*) OR TS=(testicular cancer*) OR TS=(testis cancer*) OR TS=(cancer of the testis) OR TS=(testicular malignanc*) OR TS=(scrotal cancer*)) AND (TS=(metallurgy) OR TS=(metal worker) OR TS=(foundr*) OR TS=(weld*) OR TS=(driver*) OR TS=(pilots*) OR TS=(baker*) OR TS=(miner) OR TS=(driver*) OR TS=(submarines) OR TS=(cyclist) OR TS=(cloth*) OR TS=(underwear*) OR TS=(napp*) OR TS=(sauna) OR TS=(bath*) OR TS=(hammam) OR TS=(hot tub) OR TS=(laptop*) OR TS=(paraplegia) OR TS=(tetraplegia) OR TS=(wheelchair) OR TS=(temperature*) OR TS=(hot*) OR TS=(heat*) OR TS=(hyperthermia)) NOT (TS=(cryptorchid*) OR TS=(varicocoel*) OR TS=(inguinal hernia*) OR TS=(hydrocele*) OR TS=(therap*) OR TS=(treatment*) OR TS=(orchidopexy) OR TS=(endocrine disruptor*) OR TS=(pesticid*) OR TS=(pronostic) OR TS=(ultrasound*) OR TS=(heat shock*) OR TS=(industrialysed countr*) OR TS=(fertility) OR TS=(asbestos) OR TS=(radiation*) OR TS=(genes))
SUDOC (17/09/23)	FRENCH Titre : (tumeur OU cancer OU tumeurs OU cancers) ET (testicule OU testiculaire OU testicules OU testiculaires) ET (température OU chaud OU chaleur OU vêtements OU sous-vêtements OU couches OU position assise OU sauna OU bains OU hammam OU jacuzzi OU assis OU conducteur OU pilotes OU paraplégie OU tétraplégie OU fauteuil roulant OU travaux extérieurs OU construction OU fonderie OU soudeur OU fournaise OU métallurgie OU mineur OU fours OU boulanger OU sous-marinier) ENGLISH Tile : (tumor OR cancer OR tumors OR cancers) AND (testicle OR testicular OR testis OR testicles) AND (temperature OR hot OR clothing OR underwear OR diapers OR sitting OR sauna OR baths OR hammam OR jacuzzi OR conductor OR pilots OR paraplegia OR quadriplegia OR wheelchair OR outdoor work OR construction OR foundry OR welder OR furnace OR metallurgy OR miner OR ovens OR baker OR submariner)
GOOGLE SCHOLAR (17/09/23)	FRENCH Article contenant tous les mots : cancer testicule Article contenant au moins un des mots : chaleur température vêtement assis cycliste soudeur métallurgie boulanger four construction “sous-marin” ENGLISH All articles with : testis cancer OR testicular cancer Articles with at least one word : hot temperature clothing sitting cyclist welder metallurgy baker oven construction submariner NOT treatment therapy antigen antigens

LISSA (17/09/23)	((tumeurs du testicule.tl) OU (tumeurs du testicule.mc) OU (cancer testiculaire.tl) OU (cancer testiculaire.mc) OU (tumeurs testiculaires.tl) OU (tumeurs testiculaires.mc) OU (cancer du testicule.tl) OU (cancer du testicule.mc)) ET ((travailleurs en métallurgie.tl) OU (travailleurs en métallurgie.mc) OU (Position assise.tl) OU (Position assise.mc) OU (boulanger*.tl) OU (boulanger*.mc) OU (vêtements.tl) OU (vêtements.mc) OU (chaleur.tl) OU (chaleur.mc) OU (température.tl) OU (température.mc) OU (cycliste.tl) OU (cycliste.mc) OU (four.tl) OU (four.mc) OU (construction.tl) OU (construction.mc) OU (“sous-marin”.tl) OU (“sous-marin”.mc))
CisMEF (17/09/23)	((tumeurs du testicule.ti) OU (tumeurs du testicule.mc)) ET ((professions.ti) OU (professions.mc) OU (vêtements.ti) OU (vêtements.mc) OU (industrie de la construction.ti) OU (industrie de la construction.mc) OU (bains.ti) OU (bains.mc) OU OU (chaleur.ti) OU (chaleur.mc) OU (température.ti) OU (température.mc))

VI. SUMMARY AND KEY WORDS

ENGLISH :

Introduction: Testicular cancer represents about 1% of all cancers among men. Studying the association between heat and testicular cancer becomes all the more necessary with the development of male thermal contraception methods.
Methodology: A double blind systematic review of the literature was made. The main outcome was defined by testicular cancer prevalence or incidence or association with external heat exposures. The population was composed of men without age criteria and the comparator was the general male population. A narrative analysis was made, then a quantitative analysis. The protocol was registered on PROSPERO on 17/09/2023 with the following ID: CRD42023464097.
Results: 30 original articles were selected from 372 articles eligible for analysis. Results from narrative analyses: for clothing increasing testicular temperatures, there was no significant result. For prolonged sitting position, drivers showed significant decreases in the incidence of seminoma in two studies, and pilots showed significant results but contradictory. For testicular contact to external hot sources, spa and sauna exposures showed significant negative associations with testicular cancer, whereas bathing instead of showering showed a significant positive association. For occupational heat exposures, bakers and metal industry workers showed a significant positive association with testicular cancer. Two meta-analyses were made: the first one showed a non-significant negative effect of heat exposures on the standardized incidence ratio of testicular cancer (2.6420 with IC95% = -3.0250-8.3090). The second one showed a significant positive effect of heat exposures on the association with testicular cancer (0.8912 with IC95% = 0.1683-1.6141). However, the heterogeneity was too large to come to any conclusions.
Discussion: This study cannot conclude on a link between external heat exposure and testicular cancer with the two meta-analyses carried out. However with the narrative analysis, we can hypothetise that there may be a link between external heat exposures to only high temperatures (represented by the metal industry) and testicular cancer.

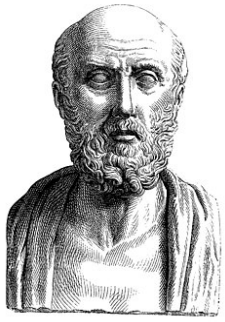
Key words: systematic review, testicular cancer, heat, temperature, occupational

FRANÇAIS :

Introduction : Le cancer du testicule représente environ 1% de l'ensemble des cancers chez l'homme. L'étude de l'association entre chaleur et cancer du testicule devient de plus en plus nécessaire avec le développement des méthodes de contraception thermique masculine.
Méthodologie : Une revue systématique en double aveugle de la littérature a été réalisée. Le résultat principal était défini par la prévalence ou l'incidence du cancer du testicule ou l'association avec des expositions à la chaleur d'origine externe. La population était composée des hommes sans critère d'âge et le comparateur était la population générale masculine. Une analyse narrative a été réalisée, suivie d'une analyse quantitative. Le protocole a été enregistré sur PROSPERO le 17/09/2023 avec l'ID suivante : CRD42023464097.
Résultats : 30 articles originaux ont été sélectionnés parmi 372 articles éligibles à l'analyse. Résultats des analyses narratives : pour les vêtements augmentant la température des testicules, il n'a pas été retrouvé de résultat significatif. Pour la position assise prolongée, les chauffeurs ont montré des diminutions significatives de l'incidence du séminome dans deux études, et les pilotes ont montré des résultats significatifs mais contradictoires. Pour le contact des testicules avec des sources de chaleur externes, les expositions aux spas et aux saunas ont montré des associations négatives significatives avec le cancer du testicule, tandis que le fait de prendre un bain au lieu d'une douche a montré une association positive significative. En ce qui concerne les expositions professionnelles à la chaleur, les boulangers et les travailleurs de l'industrie métallurgique ont montré une association négative significative avec le cancer du testicule. Deux méta-analyses ont été réalisées : la première était en faveur d'un effet positif non-significatif des expositions à la chaleur sur le ratio d'incidence standardisé du cancer du testicule (2,6420 avec IC95% = -3,0250-8,3090). La seconde était en faveur d'un effet positif significatif des expositions à la chaleur sur l'association avec le cancer du testicule (0,8912 avec IC95% = 0,1683-1,6141). Cependant, l'hétérogénéité était trop importante pour tirer des conclusions.
Discussion : Cette étude ne peut pas conclure à un lien entre l'exposition à la chaleur externe et le cancer du testicule avec les deux méta-analyses réalisées. Cependant, avec l'analyse narrative, nous pouvons émettre l'hypothèse qu'il pourrait y avoir un lien entre le cancer du testicule et une exposition à la chaleur uniquement à des températures élevées (représentées par l'industrie métallurgique).

Mots clés : revue systématique, cancer du testicule, chaleur, température, travail

VII. SERMENT D'HIPPOCRATE



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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueuse et reconnaissante envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couverte d'opprobre et méprisée de mes confrères si j'y manque !

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