Université de Poitiers

Faculté de Médecine et Pharmacie

2024

THESE

POUR LE DIPLOME D'ETAT

DE DOCTEUR EN MEDECINE

(Décret du 25 novembre 2016)

Présentée et soutenue publiquement

Le 24 mai 2024 à Poitiers

Par Madame Léa Chenard

La chaleur d'origine intra-corporelle constitue-t-elle un risque de cancer testiculaire ?
Revue systématique de la littérature

Are intracorporeal body sources of heat a risk for testicular cancer?

A systematic review

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Remerciements :

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I. TABLE DES MATIERES

I. INTRODUCTION

A. CONTEXTE

À l'heure où la France est le premier pays à inscrire l'IVG dans sa constitution, la contraception n'a jamais autant été au centre des préoccupations. Dans ce contexte, la contraception masculine gagne du terrain, avec une approche particulière suscitant à la fois intérêt et interrogations : la contraception masculine thermique. (1,2)

La contraception masculine comprend l'ensemble des méthodes et techniques utilisées pour empêcher temporairement (contraception) ou de manière permanente (stérilisation) la production de spermatozoïdes. (3)

Cette dernière, la vasectomie, consiste en une intervention chirurgicale qui implique de ligaturer, sectionner et/ou coaguler les canaux déférents au niveau scrotal afin que le sperme ne contienne plus de spermatozoïdes. (4) Malgré l'existence de techniques microchirurgicales de reperméabilisation, la vasectomie est présentée au patient comme irréversible. Comme les vésicules séminales stockent des spermatozoïdes, la méthode n'est pas immédiatement efficace. Un délai de 12 semaines est nécessaire avant de constater par un spermogramme l'absence de spermatozoïdes dans l'éjaculat. A noter qu'au niveau mondial, la ligature des trompes reste cinq fois plus fréquente que la vasectomie, quand en France, en 2022, trois stérilisations masculines ont été pratiquées pour deux stérilisations féminines.(5)

La contraception vise quant à elle à contrôler la fertilité masculine sans altérer de manière définitive les capacités reproductives et se doit de répondre à quatre critères (efficace, réversible, acceptable et de faible coût).(2)

Parmi les méthodes existantes, on retrouve l'utilisation de préservatifs, la méthode du retrait et des approches hormonales et non hormonales en développement, dont la contraception masculine thermique. (6)

La méthode hormonale consiste en l'injection intramusculaire hebdomadaire d'énanthate de testostérone. En l'absence d'étude menée à long terme sur l'utilisation de cette substance à des fins contraceptives, l'OMS limite par précaution l'emploi de cette méthode à une durée de 18 mois, mais aucune observation n'indique qu'une utilisation plus longue serait risquée. A noter que l'efficacité ne survient que trois mois après le début du traitement. Il est possible d'en vérifier l'efficacité en effectuant un spermogramme. (7)

La contraception masculine thermique repose sur le principe de l'exposition contrôlée des testicules à une température supérieure à celle du corps (2 à 3 degrés supplémentaires) pour inhiber temporairement la spermatogenèse, c'est-à-dire la production de spermatozoïdes. (8) Cette méthode s'appuie sur des dispositifs spécifiquement conçus pour maintenir les testicules à une température légèrement élevée, suffisante pour réduire la fertilité masculine sans causer de dommages permanents. On sait, en effet, aujourd'hui que plusieurs pathologies peuvent influencer la fertilité masculine en augmentant la chaleur intra-scrotale, telles que la

cryptorchidie, la hernie inguinale, la varicocèle et l'obésité. (9) Chacune de ces conditions peut altérer la fonction reproductive en affectant directement la température autour des testicules.

B. LA CONTRACEPTION MASCULINE THERMIQUE :

Le premier brevet pour un dispositif de contraception masculine thermique a été déposé aux Etats-Unis en 1967, basé sur les travaux de Rock F. et Robinson D., de l'Université de Harvard. Il s'agissait d'un dispositif, dérivé du slip suspensoir de l'homme, qui utilisait la chaleur du corps (chaleur endogène) pour augmenter la température testiculaire, en agissant comme un isolant thermique.(10) En France, une équipe de chercheurs dirigée par Mieusset R. et Bujan L. a travaillé à la mise au point d'une contraception thermique testiculaire en utilisant une nouvelle approche : suspendre les testicules et les rapprocher du corps pour augmenter leur température. (11) Certains auteurs surnomment cette méthode "cryptorchidie artificielle", cependant, comme nous le verrons, la cryptorchidie n'étant pas un simple phénomène mécanique de non-descente des testicules dans le scrotum, cette terminologie semble discutable. En effet, en établissant une analogie entre la cryptorchidie et la contraception masculine thermique, nombreux suggèrent un risque accru de cancer du testicule. Dès les années 1980, Mieusset R. et Bujan L. ont ainsi mis au point puis testé, une glissière maintenant les testicules dans le canal inguinal : slip contraceptif ou slip toulousain. (12) Le protocole est assez simple, le dispositif doit être porté 15 heures par jour. Un spermogramme est réalisé avant le début de l'utilisation puis tous les 3 mois. L'objectif, ou seuil contraceptif, est d'avoir un nombre de spermatozoïdes inférieur à 1 million/mL. Les hommes ayant des antécédents testiculaires, scrotaux, inguinaux ou spermiologiques sont exclus. Une seule grossesse non désirée a été rapportée dans l'ensemble des études, qui a été causée par une interruption du protocole. (13) Quelques études ont été menées en Egypte (Shafik et al) et aux Etats-Unis (Wang et al) dans les années 90, concluant comme Mieusset R. et Bujan L., que la contraception masculine thermique par ascension testiculaire, avait le potentiel d'être une méthode contraceptive sûre, efficace et réversible pour les hommes.(14)

Au milieu des années 2010, Labrit M. a développé un nouveau dispositif de contraception masculine thermique, remettant au goût du jour le slip toulousain. Son idée était de créer un moyen de contraception plus facile, plus intelligent et plus simple que le slip, mais basé sur le même protocole. Ce nouveau dispositif appelé Andro-switch, consiste en un anneau de silicone biocompatible et disponible en différentes tailles.(15) Le succès soudain de l'anneau contraceptif thermique, relayé par les médias français, a interpelé les autorités sanitaires françaises, les confrontant à l'absence de certification et de contrôle. (16) En décembre 2021, l'Agence nationale de surveillance du médicament (ANSM) a interdit la commercialisation et la promotion de l'anneau jusqu'à ce qu'il soit certifié comme dispositif médical à visée contraceptive par une agence de certification européenne. Cette décision sanitaire précise néanmoins que "la contraception masculine par voie thermique peut, en termes de santé publique, présenter un réel intérêt" et "que les performances et la sécurité des dispositifs médicaux "Andro-switch" (...) ont pu être évaluées dans le cadre d'une investigation clinique ; qu'il convient donc de permettre leur utilisation dans le cadre d'une investigation clinique dûment autorisée ».(17)

Cette méthode innovante n'a cependant toujours pas reçu le marquage "CE" de certification européenne, un indicateur clé de conformité avec les normes de santé et de sécurité de l'Union européenne. (18) Comme expliqué, l'absence de cette certification soulève des questions quant à l'efficacité, la sécurité et l'acceptabilité de la contraception masculine thermique. Les raisons précises de cette non-attribution ne sont pas clairement communiquées, mais elles pourraient inclure des préoccupations liées à l'utilisation prolongée de cette méthode, et la robustesse des études cliniques la soutenant, mettant ainsi en évidence d'éventuels effets secondaires ou risques associés à long terme. (19)

C. CRYPTORCHIDIE ARTIFICIELLE :

Le parallèle entre la contraception masculine thermique, souvent surnommée "cryptorchidie artificielle"(20), et la cryptorchidie elle-même est source de préoccupations. La cryptorchidie, une condition où un ou les deux testicules ne descend pas correctement dans le scrotum, est reconnue comme un facteur de risque de cancer testiculaire. (21) Cette association suscite des interrogations légitimes quant à savoir si la méthode de contraception thermique, en mimant un état similaire à la cryptorchidie, pourrait également augmenter le risque de cancer testiculaire.

La question est complexe et nécessite des investigations approfondies. La comparaison directe entre une cryptorchidie, souvent présente dès la naissance et pour une durée prolongée, et l'exposition temporaire et contrôlée des testicules, peut ne pas être entièrement pertinente. De plus, cette analogie est discutable, puisque la cryptorchidie expose les testicules pré-pubères à la chaleur du corps, alors que la contraception masculine thermique expose des testicules pubères. (22) Toutefois, la prudence est de mise, et la communauté scientifique est appelée à étudier en profondeur les conséquences à long terme de la contraception masculine thermique, notamment en ce qui concerne le risque de cancer testiculaire.

II. GENERALITES

A. ANATOMO-PHYSIOLOGIE DES TESTICULES

Les testicules sont les organes reproducteurs masculins et ont deux rôles principaux : la production de spermatozoïdes et la production d'hormones mâles. Chez l'homme adulte, les testicules mesurent environ 5 cm de long et 3 cm de large, et sont chacun contenus dans un compartiment externe appelé scrotum ou bourse, qui se trouve sous et devant le périnée.
Le testicule est entouré de nombreuses enveloppes fines (peau du scrotum, fascia dartos, fascia spermatique externe, muscle crémastérien, fascia spermatique interne, membrane vaginale, mésorchium). Attaché à la partie supérieure et postérieure du testicule, l'épididyme contient tous les tubules séminifères dans lesquels les spermatozoïdes sont produits et transportés. Les canaux efférents se terminent par le canal contourné, qui mesure 40 cm de long et s'étend de l'épididyme du testicule au canal éjaculateur de la prostate. Le canal éjaculateur contient également les vésicules séminales, qui sont des réservoirs de sperme où les spermatozoïdes s'accumulent entre les éjaculations successives. (23)

1. THERMORÉGULATION DES TESTICULES

La meilleure température pour la maturation des cellules germinales dans le tractus séminifère est de 2 à 8°C en dessous de la température corporelle, qui est d'environ 36,5°C. (24) Plus précisément, la chaleur testiculaire se situe entre 31°C et 36°C, en fonction des méthodes de mesure de la chaleur et de l'absence ou de la présence de pathologies. (25)
Il existe deux systèmes anatomiques de régulation de la température testiculaire :
- Le scrotum : possède des propriétés naturelles de perte de chaleur grâce à ses caractéristiques physiques. Le scrotum est en effet dépourvu de graisse sous-cutanée (principalement de la graisse brune et beige, qui peut augmenter la chaleur locale). (26) Le scrotum est également entouré de nombreuses enveloppes fines, dont les muscles dartos et crémastériens, qui répondent efficacement aux changements de la température ambiante. En outre, la chaleur est probablement évaporée par les glandes apocrines de la peau du scrotum, bien que cela soit encore remis en question chez l'homme. (27) L'activation de ces récepteurs de chaleur se produit à un seuil spécifique et induit des réponses réflexes locales et générales. (28)
- Le plexus pampiniforme : ce deuxième système thermorégulateur est situé dans le cordon spermatique. Ce plexus est un site d'échange de chaleur entre le sang artériel entrant par l'artère testiculaire tortueuse et le sang veineux sortant par les multiples veines qui l'entourent, permettant un pré-refroidissement du sang artériel provenant du testicule. (29)

2. EFFETS DE L'EXPOSITION DES TESTICULES A LA CHALEUR

La chaleur peut causer plusieurs dommages aux testicules :

- Modifications de l'expression des gènes : l'expression des gènes peut être modifiée par le stress thermique, en particulier les gènes codant pour l'arrêt cellulaire et l'augmentation de l'apoptose (HSF1, p53, caspases). Elle peut également inhiber les gènes codant pour la réparation cellulaire (Bag-1, protéines de liaison à l'ARN Cirp, ADNpolymérase β et ADN ligase III). Il faut noter qu'après quelques heures de stress thermique, certains gènes pro-apoptotiques peuvent être régulés à la baisse pour éviter la destruction de toutes les cellules.(30)
- Activation des voies oxydatives : L'équilibre oxydatif des cellules est lié à des mécanismes pro-oxydants contrebalancés par des mécanismes anti-oxydants. (31) Le principal mécanisme pro-oxydant implique la production d'espèces radicalaires (ou réactives) de l'oxygène, connues sous le nom de ROS. Par définition, ces radicaux libres sont des espèces chimiques dotées d'un seul électron sur leur strate périphérique, ce qui les rend extrêmement instables et très réactifs. Ils contribuent à endommager l'ADN, les protéines et les lipides. Pour maintenir ces radicaux à un niveau acceptable, des antioxydants naturels sont présents dans les testicules (vitamines C, vitamine E et caroténoïdes). Lorsque cet équilibre oxydatif est rompu, le stress oxydatif entraîne l'apoptose cellulaire et le dysfonctionnement des spermatozoïdes. (32) Les ROS pourraient intervenir de deux manières dans la réponse au stress thermique : une activation directe de l'apoptose par l'oxydation de composants cellulaires tels que l'ADN et les lipides, et une activation indirecte de l'apoptose par des voies de régulation activées par les ROS. (33)
- Activation des voies de l'apoptose cellulaire : l'exposition des cellules germinales testiculaires à un stress thermique peut provoquer des changements dans l'expression des gènes, des dommages à l'ADN ou une autophagie programmée par la cellule conduisant à l'apoptose cellulaire. (34) Les protéines effectrices de l'apoptose (caspases 3,6,9) peuvent être activées par deux voies de signalisation : une voie intrinsèque dépendant de la mitochondrie et des protéines Bax/Bcl2, et une voie extrinsèque dépendant de la membrane cellulaire et des protéines Fas/FasL. (25)

- Diminution de la spermatogenèse : la spermatogenèse est le processus de production des spermatozoïdes et implique une série complexe d'étapes pour produire des spermatozoïdes fonctionnels. (35) Elle se déroule dans les tubules séminifères du testicule et dure environ 74 jours. Le processus de spermatogenèse se déroule idéalement à 2°C en dessous de la température centrale du corps. (36) Dès 1922, Crew et son équipe ont suggéré que l'exposition des testicules à la chaleur pouvait entraîner une réduction de la spermatogenèse. (37) La relation entre température et spermatogenèse a été mise en évidence dans les années 1960, puis de nombreuses études se sont intéressées au lien entre la chaleur et l'infertilité. (38) En 2022, une méta-analyse a démontré que le stress induit par la chaleur réduisait le nombre et la qualité des spermatozoïdes. (39)

B. LE CANCER TESTICULAIRE :

Le cancer du testicule est le premier cancer de l'homme jeune et représente 1 à 1,5 % des cancers de l'homme tout âge confondu. (40) Il s'agit pourtant d'une tumeur rare (1 à 2% de l'ensemble des cancers), caractérisable en deux points : l'âge jeune du diagnostic (entre la puberté et 45 ans majoritairement, avec un âge médian du diagnostic à 36 ans), et le bon pronostic avec près de 90% de guérison à 5 ans, variant peu avec l'âge du diagnostic. (41) Environ 2 700 nouveaux cas de cancer du testicule sont enregistrés en France chaque année selon une estimation réalisée par l'institut national du cancer. (42) Dans le testicule se trouvent deux types de cellules : les cellules germinales, qui produisent les spermatozoïdes et les cellules dites non germinales. (43) Il existe différents types de cancer du testicule selon les cellules concernées. Les tumeurs germinales, les plus fréquentes avec deux sous-types : les tumeurs séminomateuses (ou séminome) qui représentent 30 à 40% des cas et touchent les hommes entre 35 et 45 ans et les tumeurs non séminomateuses (choriocarcinome et/ou tumeur vitelline et/ou carcinome embryonnaire et/ou tératome) qui représentent 60 à 70% des cas. (44) Les tumeurs non germinales (tumeurs à cellules de Leydig ou à cellules de Sertoli, sarcomes) sont beaucoup plus rares (5% des cas). (45)

Facteurs de risque et facteurs associés :

Les nombreux facteurs qui sont susceptibles d'influencer la formation des tumeurs testiculaires, leur variabilité et les différents moments où ils peuvent s'exprimer au cours du développement expliquent en grande partie la complexité de l'épidémiologie du cancer testiculaire.(46)
Parmi les facteurs de risque les mieux documentés dans les études épidémiologiques, on retrouve un antécédent personnel de cancer testiculaire et la cryptorchidie. (47) Le risque de cancer testiculaire étant augmenté à la fois dans le testicule cryptorchide et dans le testicule controlatéral non cryptorchide. (48)(49) De plus, la correction chirurgicale (abaissement intra-scrotal) ne semble pas corriger ce risque supplémentaire quel que soit l'âge auquel elle est effectuée, bien que ce soit encore discuté par certains. (50) D'autres études ont identifié plusieurs facteurs de risque et pathologies qui pourraient augmenter le risque de cancer testiculaire, notamment les antécédents familiaux de cancer testiculaire, (51) les anomalies génétiques (telles que le syndrome de Klinefelter, le syndrome de Down), (52,53) l'exposition

à des agents chimiques (une exposition professionnelle à certains agents chimiques, tels que les pesticides, les solvants organiques et d'autres substances toxiques), (54,55) les traumatismes testiculaires, le port de sous-vêtements serrés et un statut social élevé. (56–58)

L'hyper-oestrogénie maternelle est un facteur qui a été suggéré dès 1983 par Henderson, avec la survenue d'une élévation transitoire des oestrogènes libres intra testiculaires lors du début de la différenciation des cellules germinales lors de la vie intra-utérine. (59) Il avait alors suggéré que cette anomalie altérait définitivement les cellules gonadiques qui n'étaient réactivées que lors de la puberté, par la stimulation des gonadotrophines, expliquant ainsi le pic maximal de développement des tumeurs testiculaires après la puberté. (60) De plus, il existe une association nette entre des marqueurs d'une hyper-oestrogénie maternelle lors de la grossesse et le risque de cancer testiculaire chez les enfants. (61) En effet, le risque est plus élevé chez les enfants dont la mère présente un surpoids (par aromatisation excessive de testostérone dans la graisse).(62)

Les autres facteurs maternels qui ont été mis en évidence jouent un rôle très modéré. Les seuls ayant un lien significatif sont les métrorragies du premier trimestre, la taille de la fratrie et la parité, le risque de développer un cancer testiculaire étant d'autant plus élevé que le rang de naissance de l'homme est élevé ou que ses frères et sœurs sont plus nombreux. (63)

D'autre part, des études ont suggéré un lien entre l'infertilité masculine et un risque accru de cancer testiculaire. (64)

Enfin, l'atrophie testiculaire (idiopathique ou secondaire), la hernie inguinale, les infections virales sont des facteurs qui ont parfois été associés à un risque plus important de cancer testiculaire, mais leur impact réel est encore largement hypothétique et discuté, en dehors des atrophies testiculaires. (65,66)

C. CONTRE-INDICATIONS A L'UTILISATION DE LA CONTRACEPTION MASCULINE THERMIQUE :

En l'absence de toute étude clinique réalisée jusqu'alors, il n'est pas recommandé d'utiliser la contraception masculine thermique chez les hommes ayant des antécédents d'anomalies de la descente des testicules (cryptorchidie, ectopie) traitées ou non, de hernie inguinale traitée ou non, ou de cancer du testicule. (67) Toujours par précaution, une grande obésité ou la présence d'une varicocèle de grade 3 sont pour le moment des contre-indications à cette méthode. (68) En établissant une analogie entre cryptorchidie et CMT, certaines voix suggèrent un risque accru de cancer testiculaire chez les utilisateurs de la CMT. (69) Comme évoqué cette analogie reste discutable, puisque la cryptorchidie, présente depuis la naissance, expose les testicules pré-pubères à la chaleur corporelle pour une durée souvent prolongée, quand la contraception masculine thermique expose les testicules matures, à une chaleur modérée. (70).

En attendant, le temps de mener les études et le suivi post-commercialisation nécessaires, une revue de la littérature scientifique devrait déjà permettre de se prononcer sur le niveau de probabilité d'un lien entre la chaleur intra scrotale et endogène, et la survenue d'un cancer du testicule.

Le lien entre cancer testiculaire et cryptorchidie ayant déjà fait l'objet de revues systématiques de la littérature, (71–73) nous pensions exclure la cryptorchidie dans un premier temps, cependant il nous a semblé pertinent d'inclure les articles portant sur la cryptorchidie afin de voir si certaines études s'étaient intéressées à la chaleur induite par la cryptorchidie dans la cancérogénèse testiculaire. Ainsi nous avons également décidé d'inclure les études s'intéressant aux syndromes urogénitaux incluant la cryptorchidie, comme le syndrome de dysgénésie testiculaire, pour être le plus exhaustif possible. (74,75)

Nous avons ensuite sélectionné les pathologies autre que l'existence d'un testicule ectopique, et le cancer testiculaire, contre indiquant l'utilisation de la CMT, telles que la hernie inguinale, la varicocèle, et l'obésité. (67) Ces pathologies, étant susceptibles d'augmenter la température scrotale, nous avons ainsi également inclus deux autres pathologies suspectées de modifier la température testiculaire : l'hydrocèle et les infections uro-génitales (telle que l'orchi-épididymite).(76,77)

L'étude sur la température testiculaire chez les hommes menée par Taichi Kitayama de l'Université de Kyoto a analysé la mesure des températures dans différentes régions du corps chez des patients masculins, en mettant l'accent sur la température testiculaire. L'étude a été réalisée sur 141 patients, âgés de 10 à 76 ans. Les températures du rectum, du testicule, de la cavité scrotale et de la région de l'anneau inguinal externe ont été mesurées. Les patients ont été répartis en deux groupes : testicules sains et pathologies scrotales. Des cas spécifiques, tels que l'orchite, les inflammations épididymaires et les anomalies testiculaires tels que la varicocèle et la hernie inguinale, ont également été examinés pour évaluer leur impact sur la température testiculaire, mettant en évidence des différences de température significatives entre ces groupes.(78)

Pour approfondir notre compréhension des contre-indications à l'utilisation de la méthode contraceptive thermique, il est essentiel de se pencher sur certaines pathologies pouvant influencer la température intra testiculaire. (79) La cryptorchidie, la hernie inguinale, la varicocèle, et l'obésité sont des conditions connues pour leur impact sur la température testiculaire, tandis que l'hydrocèle et les antécédents d'infections ou d'inflammations génitales, tels que l'orchi-épididymite, semblent, étant donné leur physiopathologie, pouvoir également jouer un rôle dans la thermorégulation testiculaire. (80–82)

Pathologies sources endogènes de chaleur intrascrotale :

Explorons la physiopathologie des différentes affections mentionnées et leur lien avec l'augmentation de la chaleur intra-testiculaire.

- **CRYPTORCHIDIE :**

A partir du 3e mois in utero, les testicules migrent à travers le canal inguinal, le long d'une évagination du péritoine appelée canal péritonéo-vaginal. Cette évagination va laisser subsister un reliquat : la vaginale. La cryptorchidie est une anomalie de migration embryologique du testicule. (83) Elle correspond à un arrêt de migration sur le trajet normal entre l'aire lombaire et le scrotum. Elle est à distinguer de l'ectopie testiculaire (testicule en dehors du canal de migration physiologique). Le plus souvent unilatérale, elle peut être bilatérale. Il s'agit d'une des anomalies congénitales les plus courantes du système génital masculin. Cette condition peut altérer le développement normal et la fonction des testicules en exposant les tissus testiculaires à une température corporelle plus élevée que celle du scrotum, optimale pour la spermatogenèse. (84) Cette exposition à une température supérieure peut endommager le tissu testiculaire et augmenter le risque de cancer testiculaire. (85) De plus, même après une prise en charge chirurgicale, par orchidopexie, des effets sur la fertilité et la qualité du sperme peuvent persister. (86)

En effet, la chaleur scrotale peut également jouer un rôle dans les modifications histologiques observées dans les testicules avec cancer. (87) Des études ont montré que l'exposition à des températures élevées, comme celles causées par la cryptorchidie ou d'autres conditions qui augmentent la chaleur dans le scrotum, peut affecter négativement la spermatogenèse et augmenter le risque de mutations génétiques, majorant ainsi le risque de cancer testiculaire. (88) Par conséquent, en plus des altérations du développement fœtal, la chaleur scrotale peut également contribuer aux changements histologiques observés dans les testicules associés au cancer testiculaire. (89,90)

L'hypothèse du syndrome de la dysgénésie testiculaire (TDS) propose qu'une proportion des troubles de la reproduction masculine - cryptorchidie, hypospadias, infertilité et cancer testiculaire - peuvent être des symptômes d'une maladie développementale sous-jacente, le TDS, qui est très probablement le résultat d'un développement gonadique perturbé dans l'embryon. (91,92) Le TDS peut être causé par des facteurs génétiques, des facteurs environnementaux ou liés au mode de vie, ou une combinaison de ces différents facteurs.(74)

- **HERNIE INGUINALE :**

Une hernie inguinale se produit lorsque du tissu, souvent une partie de l'intestin, fait saillie à travers une zone de faiblesse dans les muscles abdominaux, au niveau de l'aine. Bien que le lien direct entre la hernie inguinale et l'augmentation de la température intra-testiculaire ne soit pas clairement établi dans la littérature scientifique, la présence d'une hernie pourrait par conséquent augmenter la température dans la région inguinale et, par extension, influencer la température scrotale et testiculaire. (93–95) La pression et la proximité avec le canal inguinal peuvent théoriquement perturber la thermorégulation normale. (96)

- **VARICOCELE :**

La varicocèle est une dilatation variqueuse des veines spermatiques, survenant à gauche dans 90 % des cas par une insuffisance valvulaire à l'abouchement de la veine spermatique gauche qui se jette dans la veine rénale gauche (la droite se jette directement dans la veine cave inférieure), responsable d'une augmentation du volume testiculaire par stagnation de la vascularisation (97), pouvant conduire au trouble de la régulation de la température locale scrotale, entrainant ainsi une augmentation de cette dernière, et altérant potentiellement la spermatogenèse.(98)

Dans les études épidémiologiques, la fréquence de la varicocèle peut aller jusqu'à 22 % des hommes de la population générale. Cette anomalie est plus fréquente chez les hommes ayant un trouble de la fertilité, atteignant 40 % pour ceux ayant une anomalie du spermogramme.(99)

Certaines études ont observé des températures testiculaires plus élevées du côté gauche chez les patients atteints de varicocèle par rapport aux volontaires sains. Ainsi, la varicocèle est associée à une altération de la fonction testiculaire, à une réduction de la qualité du sperme et peut affecter la fertilité masculine.(100) L'augmentation de la température intra-testiculaire est un facteur clé dans ces effets. En effet, certaines études mentionnent des liens potentiels entre les asymétries thermiques du scrotum et le risque de cancer testiculaire. (101)Il est noté que des températures testiculaires et scrotales plus élevées, en particulier du côté gauche, pourraient avoir des implications sur l'incidence et le développement de la varicocèle, mais aussi du cancer testiculaire. (102)

- **OBESITE :**

L'obésité est définie par un Indice de Masse Corporelle supérieur à 30kg/m2. (103) Le surpoids peut augmenter la quantité de tissu adipeux au niveau inguinal, mais aussi en regard des organes génitaux externes et plus particulièrement autour du scrotum. Agissant comme un isolant thermique et pouvant réduire la dissipation de la chaleur, le tissu adipeux modifie la régulation de cette dernière et peut entrainer l'augmentation de la température intra-scrotale. (104) En augmentant la température scrotale, et en modifiant ainsi l'environnement thermique idéal à la production de spermatozoïdes, l'obésité influence potentiellement la fertilité. De plus, l'obésité est souvent associée à des déséquilibres hormonaux qui peuvent eux-mêmes affecter la fonction testiculaire. (105)

- **HYDROCELE :**

L'hydrocèle est un épanchement liquidien péri-testiculaire et intravaginal. Chez l'enfant, elle est due à la persistance du canal péritonéo-vaginal, on parle alors d'hydrocèle communicante. (80) Elle est physiologique à la naissance, et le canal peut se fermer spontanément jusqu'à l'âge de 12 - 18 mois.(106) Chez l'adulte, elle est le plus souvent idiopathique et due à une sécrétion liquidienne excessive par la vaginale. (107)

Bien que la littérature scientifique ne mentionne pas spécifiquement une augmentation de la température testiculaire due à l'hydrocèle, l'accumulation de liquide, et donc du volume scrotal peut théoriquement modifier la thermorégulation locale en agissant comme un isolant, ce qui pourrait affecter la spermatogenèse. (108–110)

- **INFECTIONS URO-GENITALES (ORCHI-EPIDIDYMITE ET ORCHITE) :**

L'orchi-épididymite est une infection ou une inflammation du testicule et de l'épididyme, d'origine sexuelle dans le cadre d'une infection sexuellement transmissible (deux germes incriminés, Chlamydia trachomatis et Neisseria gonorrhoeae), urinaire (infection par voie rétrograde dont les germes les plus souvent retrouvés sont Escherichia coli, Staphylococcus aureus ou entérocoques) ou virale dans le cadre de l'orchite (habituellement due au virus des oreillons), pouvant entraîner une augmentation de la température locale en raison du processus inflammatoire. (111) En effet, les zones inflammatoires sont le siège d'une activité thermogénique accrue, parfois associées à des foyers hyperthermiques dans la région inguino-scrotale. (112–115)

Cette élévation de la température locale peut altérer la fonction testiculaire et la fertilité par la perturbation de l'environnement optimal pour la spermatogenèse mais aussi conduire à d'autres complications, soulignant l'importance d'un diagnostic et d'un traitement appropriés pour maintenir la santé reproductive masculine. (85,116)

Chacune de ces pathologies soulève des préoccupations importantes concernant l'utilisation de la contraception masculine thermique.

III. ARTICLE:

A. INTRODUCTION:

Testicular cancer represents a unique clinical challenge in the contemporary medical landscape. In fact, testicular carcinoma stands as the most prevalent solid malignancy among young men aged 14 to 44 years, making it significant health concern worldwide. (117)

Over the past three decades its global incidence has shown marked increases, particularly in industrialized regions (such as North America, Europe, and Oceania). (42,118,119)
Fortunately, currently treatments exhibit remarkable efficacity, ensuring a 5-year disease-free survival rate in nearly 95% of patients. (120,121)
This complex and multifaceted scenario requires a great deal of effort to understand the clinical base of available evidence. Epidemiological studies have identified various risk factors, or associated factors, including cryptorchidism (most well established and documented) (59,122,123), the presence of a contralateral testicular tumor (124), testicular injury (125), wearing of tight-fitting underclothing (63), maternal use of exogenous estrogens during pregnancy (126), higher socioeconomic status (127), and professional occupations. (128,129)
Two etiological hypotheses emerge: a relative hormone imbalance, particularly an excess of estrogen, and a disruption of testicular thermal regulation. (130,131) While exposure to heat as a risk factor for testicular cancer has been investigated in the past, studies were few and discordant, requiring further investigation.(132)

In addition to this debate surrounding testicular cancer, another subject is taking center stage: male contraception.
Even more interesting with the development of male thermal contraception. The first experimental contraception device started in the 1980s and kept improving until the recent Androswitch ring. (11) Indeed, in 2017, Labrit M. developed this biocompatible silicone ring, bringing up to date the contraceptive slip.(15)
Despite promising advancements, none of the male thermal contraception devices has obtained the European Certification (CE) marking yet, guaranteeing efficacy and safety. (133) In 2021, the French National Agency for the Supervision of Medicines (ANSM) banned the marketing and promotion of the ring until it had been certified as a medical device for contraceptive purposes by the European certification Agency. (17)

These methods often nicknamed “artificial cryptorchidism”, use the 2-3 degree increased in intra-testicular heat, induced by the suspension of the testes, mimicking cryptorchidism, a condition associated with elevated testicular cancer risk. (20,134)
Moreover, about 10% of all cases of germ cell tumors occur in men with a history of cryptorchidism, with the most accredited hypothesis related to the elevated temperature of the undescended testis. (135)
While the analogy between cryptorchidism and male thermal contraception requires scrutinity studies, it shows the importance of investigating the potential link between heat exposure and testicular cancer.

Through a systematic review of the literature, this study aims to elucidate the relationship between intra-testicular exposure to supra physiological temperatures and an increased testicular cancer risk.

B. METHODOLOGY:

The protocol was registered on PROSPERO (international prospective register of systematic reviews) on 17/09/2023 with the following ID: CRD42023464097. The study had neither funding nor conflicts of interest.

1. OUTCOMES:

Main outcome of the study is defined by testicular cancer prevalence or incidence or association with any type of heat exposure. The measures of effect used are odds ratios (OR), relative risks (RR), hazard ratios (HR), and standardized incidence ratios (SIR). Testicular cancer diagnoses were defined by an evocative imagery, or an evocative anatomopathology, or data from an Institutional cancer registry. Secondary outcomes were defined by the minimal exposure duration until the occurrence of testicular cancer, the minimal threshold of temperature necessary to the occurrence of testicular cancer, and the subtype of testicular cancer.

2. 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.

3. INTERNAL HEAT EXPOSURES:

We have selected the pathologies that contraindicate the use of the thermal male contraceptive method, and any scrotal pathologies likely to increase testicular heat. 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. (136) Therefore, in our study, we used the testicular heat exposures explored in infertility studies.

The association between testicular cancer and cryptorchidism has already been the subject of plural systematic literature review. (22,137,138) Initially, we considered excluding cryptorchidism, however, it seemed relevant to include articles on cryptorchidism to investigate if certain studies had focused on the heat induced by cryptorchidism in testicular carcinogenesis. Therefore, we also decided to include studies focusing on urogenital syndromes involving cryptorchidism, such as Testicular Dysgenesis Syndrome (TDS) and Duct Syndrome, to be as comprehensive as possible. (74,139)

Subsequently, we selected pathologies other than the presence of an ectopic testicle and testicular cancer, which contraindicate the use of thermal male contraception (TMC), such as inguinal hernia, varicocele and obesity. (67,133) Like cryptochrodism, varicocoele is related to

a continuous elevation in testicular temperature. (140) Zorgniotti and MacLeod found that men with varicocele had a scrotal temperature of 0.6°C–0.8°C above that of a control group. (141) These pathologies, which are likely to increase scrotal temperature, led us to also include two other pathologies suspected of altering scrotal temperature : hydrocele and uro-genital infections (including orchid-epididymitis). (107,112,142,143)

4. 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. REVMAN 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 case-control studies and non-randomized cohorts. 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 intrascrotal heat exposure (cryptorchidism, inguinal hernia, varicocele, obesity, hydrocele, and uro-genital infections) according to the studies inclusion and exclusion criteria and bias assessment.

Table 1 : Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Main outcome : testicular cancer prevalence or incidence or association with any type of heat exposure - Intra-corporeal (endogeneous) heat exposures : (Contraindications to the use of MCT, testicular and scrotal diseases, known or suspected, to increase testicular temperature) . Cryptorchidism (pathophysiology of the increased scrotal temperature induced by cryptorchidism) . Inguinal hernia . Varicocele . Obesity, overweight . Hydrocele . Uro-genital infection or inflammation, Orchitis, orchi-epididymitis, - Population : Men without age criteria - Comparator : general male population	Population : women, animals Studies : . Non original paper (review, letter), case report . Full text in an other language than French or English

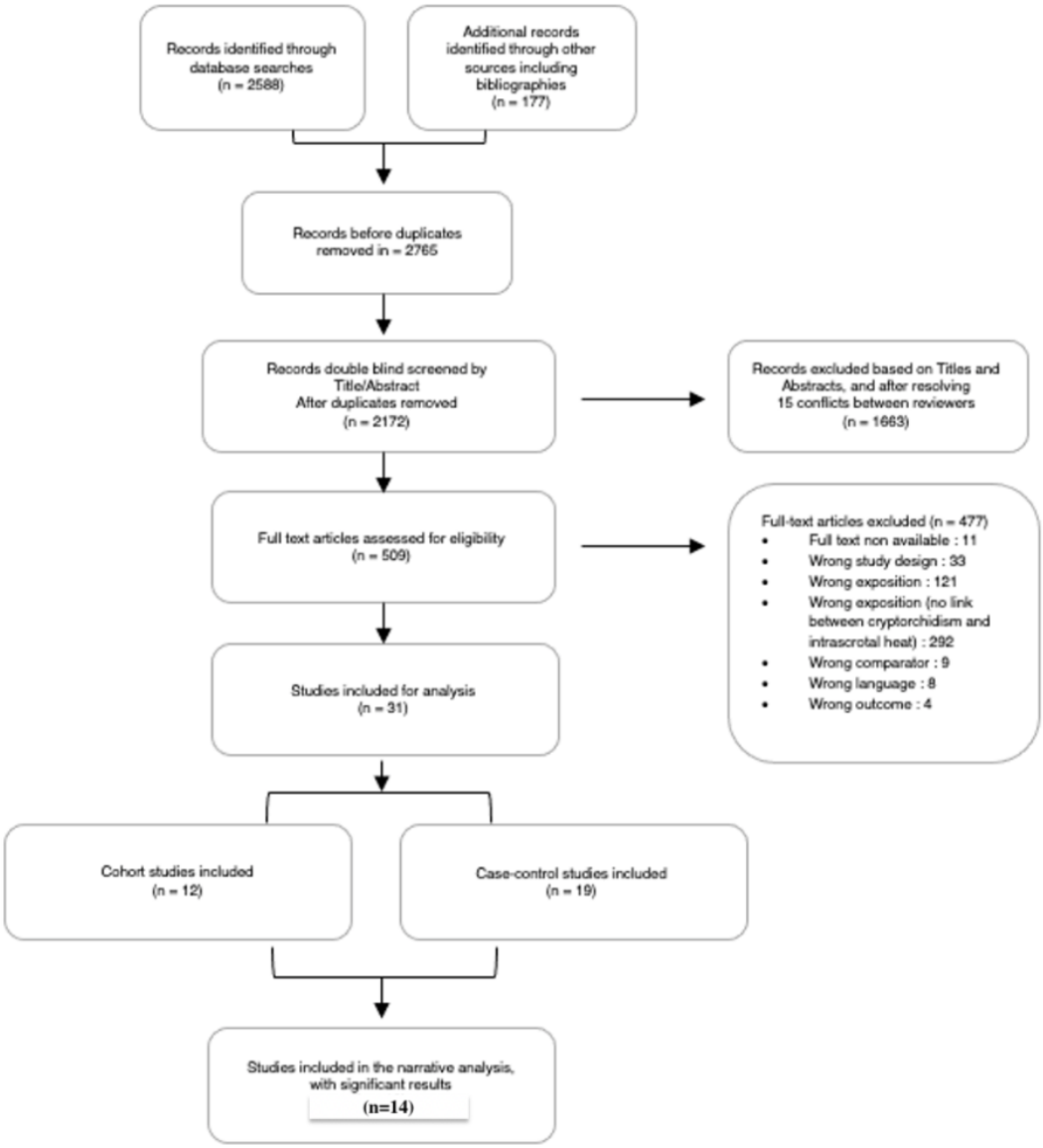
C. RESULTS

1. SCREENING :

Results from search queries came to 2588 articles, among which duplicates (522 articles from Pubmed, 931 articles from Embase, 107 articles from Cochrane, 866 articles from Web of Science, 18 articles from Sudoc, 37 articles from Google Scholar, 11 articles from Lissa, 96 article from CisMEF). In addition to this, there were 177 articles added to the analyses through other resources.

After the first screening (by Title and Abstract) it remained 509 articles. After the second screening (after reading Full texts) it remained 31 articles, from which 14 articles with significant results were included in the narrative analysis.

Figure 1 : Flow chart



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2. ALL RESULTS FROM PRIMARY ANALYSIS :

All results are summarized in tables following extraction data from the 31 included articles: 12 were non randomized cohort studies (Table 2) and 19 were case-control studies (Table 3).

Table 2 : Case-control studies (19 studies).

Tables 3 : Cohort studies (12 studies).

Only significant results are summarized following extraction data from 14 studies, and ranked by heat exposures (Table 4).

Table 4 : Only significant results.

Table 2 : Case-control studies (19 studies).

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
1) Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia, Linda M. Pottern, 1985. USA	Case-control study. Included 271 cases of testicular cancer and 259 controls,men aged 18-42 years, all referred to three collaborating medical centers in the Washington DC area, to assess the relative risk associated with a history of undescended testis and hernia repair.	Cryptorchidism	Association between increased temperature related to cryptorchidism and testicular cancer	RR=3,7 (IC = 1,6-8,6)	This study aimed to investigate the relationship between cryptorchidism (undescended testis) and the risk of testicular cancer among young men. The research was conducted through a case-control study involving men aged 18-42 who were referred to three medical centers in the Washington, DC area. Testicular cancer cases diagnosed between 1976 and 1981 were compared with controls diagnosed with cancers other than genital tract cancer during the same period. The study found a significant association between a history of cryptorchidism and testicular cancer, with a threefold increased risk for men who had undergone orchiopexy (surgical correction of undescended testis). The risk of testicular cancer was observed to increase with age at correction of cryptorchidism, indicating a direct relationship between the age of corrective surgery and cancer risk. The analysis also revealed a lack of elevation in risk for the contralateral testis, suggesting that internal factors affecting the retained testis in the body may be responsible for the increased cancer risk, rather than a congenital predisposition. Furthermore, the study highlighted the potential role of increased testicular temperature or other exposures related to the presence of an undescended testis in the body in contributing to the elevated risk of testicular cancer. These findings support the recommendation for early surgical correction of cryptorchidism to reduce the risk of testicular cancer, and underscore the importance of understanding the mechanisms linking cryptorchidism, testicular cancer, and the impact of corrective surgery on cancer risk.
		Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	Inguinal hernia before 7 years old: RR = 1,5 (IC 95% : 0,8-2,7) Inguinal Hernia after 7 years old: RR = 6,1 (IC 95%: 1-43,9)	The study, conducted in the Washington, DC area, aimed to investigate the relationship between cryptorchidism, inguinal hernia, and the risk of testicular cancer in young men aged 18-42. A large case-control study was carried out involving 271 cases of testicular cancer and 259 controls. Subjects were selected from three collaborating medical centers, and detailed information was obtained through interviews and medical records. The study found a higher risk of testicular cancer in men with a history of undescended testes, especially if the condition was not corrected. Additionally, men who underwent hernia surgery after age 7 had an elevated risk of testicular cancer on the same side as the hernia. The study found that there was no substantial excess risk of testicular cancer for men without cryptorchidism who had undergone hernia repair. However, for those who had hernia repair at older ages (28 years and above), there was an elevated risk of testicular cancer on the same side as the hernia. This elevated risk was particularly notable for bilateral hernia repairs. The study suggests that this increased risk may be due to delayed correction of undescended testes or other factors related to late hernia repair. The study highlighted that while previous research had shown a relationship between inguinal hernia and testicular cancer risk, the association was not well-defined. The study proposed several explanations for this finding, including the possibility of chance, the impact of late correction of undescended testes among individuals with both hernia and cryptorchidism, or the potential risk elevation due to delayed correction. The study supported the importance of early surgical correction of cryptorchidism and inguinal hernia to reduce the risk of testicular cancer.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999. United Kingdom	Case-control study. Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas. Controls were selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	Inguinal hernia	Association Inguinal hernia (risk factors) and testicular cancer	Inguinal hernia (all): For pure seminoma tumors: OR = 1.60 (95% [CI]: 0.88-2.93) for other histological types of tumors: OR = 2.39 (95% CI: 1.28-4.46). Inguinal hernias diagnosed before the age of 15 : for pure seminoma : OR = 3.12 (95% CI: 1.42-6.88) for other histologies : OR = 2.49 (95% CI: 1.06-5.88) Inguinal hernias diagnosed After the age of 15 : for pure seminoma : OR = 0,56 (95% CI: 0,2-1,6) for other histologies : OR = 2.28 (95% CI: 0,93-5,56)	This study, one of the largest studies on the aetiology of testicular germ cell tumours, explores the association between testicular germ cell tumors by histological tumor type, and risk factors, including factors like undescended testis, age at puberty, and exercise habits. The analysis by histological tumour type reveals significant differences in risk factors, providing insights into the aetiology of different tumour types. The study methodology involved interviews, medical history reviews, and pathology report analyses to classify tumours as 'pure seminoma' or 'other histological type'. The study used unconditional logistic regression to estimate odds ratios and identify risks that differed significantly by tumour type. The OR for inguinal hernia were similar for pure seminoma and other tumours, however, when subdivided by age at diagnosis of hernia. Risks were raised, and of similar magnitude, for hernias diagnosed before the age of 15, whilst for hernias diagnosed later than this the risk was increased (no significant) for non-seminoma tumours (OR = 2.3), but reduced (no significant) for pure seminomas (OR = 0.6). These results suggest a potential association between inguinal hernia and an increased risk of testicular germ cell tumors, particularly for certain histological types. The results highlight the importance of considering histological differences in understanding testicular cancer risk factors. The risks associated with inguinal hernias were similar overall for both histological groups, but analysis by age at hernia diagnosis revealed different risk patterns.
3) Congenital malformations and testicular germ cell tumors, Britton Trabert, 2013. Sweden	Population-based case-control study. Included individuals diagnosed with testicular germ cell tumors (cases) and matched controls without the tumors.	Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	OR =1,37 (IC 95%: 1,11-1,68)	The study was conducted in Sweden using population-based registry data. It aimed to investigate the association between congenital malformations and testicular germ cell tumors (TGCT). A total of 7,552 TGCT cases diagnosed between 1964 and 2008 were included, along with 32,955 controls matched for year and county of birth. Hospitalization records were used to identify congenital malformations, and statistical analysis was performed using conditional logistic regression. The study found that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, are associated with an increased risk of testicular germ cell tumors (TGCT) . Specifically focusing on inguinal hernia, the analysis revealed that there is an elevated risk of TGCT associated with inguinal hernia, even after accounting for the association between cryptorchidism and TGCT . This suggests that inguinal hernia may independently contribute to the risk of developing testicular cancer. The study highlighted that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, were linked to an increased risk of testicular germ cell tumors (TGCT), supporting the notion that prenatal exposures affecting proper genital development may play a role in TGCT etiology. The study found that hypospadias, inguinal hernia, and other genital malformations were associated with an increased risk of TGCT, supporting the hypothesis that prenatal exposures affecting proper genital development may be related to the development of these tumors.The findings also suggested that the associations between these abnormalities and TGCT risk may represent distinct etiologic pathways, with inguinal hernia showing consistent increased risks across various studies . Additionally, the study discussed the potential implications of early diagnosis of malformations, such as hypospadias, on the severity of defects and their relation to TGCT risk.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
4) Cryptorchidism, hernia, and cancer of the testis. Alan S. Morrison, 1976. USA	Case-control Study. 596 patients with testicular cancer and 602 unaffected controls, who had served in the U.S. military between 1950 and 1970, were studied based on the medical histories and military records of the participants.	Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and testicular cancer	RR: 2,9 (IC à 95%: 1,3-7,0)	The study focused on young adults serving in the Army, and the data collection process ensured that information on undescended testis and other exposures was obtained consistently for cases and controls. The risk ratio estimate for testicular cancer associated with undescended testis was 8.8, with previous studies suggesting a risk ratio closer to 10.The study found that men with a history of undescended testis had a significantly higher risk of testicular cancer, with a risk ratio estimate of 8.8. Additionally, individuals who had undergone hernia operation before age 15 were 2,9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed. Furthermore, undescended testis was closely associated with the side of the testicular tumor, with tumors often occurring in the testis that had been undescended. Histologically, tumors in patients with undescended testis were more likely to be seminomas compared to other types of tumors. The data suggested a moderate elevation of risk among subjects with repaired hernias, indicating a potential link between inguinal hernia and testicular cancer risk. Further research is warranted to explore the relationship between inguinal hernia and the risk of testicular cancer in more detail. The discussion highlighted three peaks in testicular cancer morbidity and mortality: at 2 years of age, early adulthood, and old age. The study also discussed the potential causal relationship between undescended testis and testicular cancer, emphasizing the need for further research, especially regarding the impact of surgical correction of undescended testis on testicular cancer rates. The study found a significant association between undescended testis and an increased risk of testicular cancer, with a risk ratio estimate of 8,8. Individuals who had undergone hernia operation before age 15 were 2,9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed, and hernia was not associated with tumors of a specific histologic type.
5) Genital anomalies and risk for testicular cancer in Danish men. A Prener, 1996. Denmark	Case-control study. 183 cases of testicular cancer registered in the Danish Cancer Registry. For each case, 2 age- and sex-matched controls were selected, resulting in a total of 366 controls. In a cohort of Danish boys characterized by being born between 1941 and 1957, having attended schools in a defined area of Denmark, and having a school health record available.	Inguinal hernia	Association between urogenital abnormalities and testicular cancer	Inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7)	In a cohort of Danish boys characterized by being born between 1941 and 1957, having attended schools in a defined area of Denmark, and having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985. We selected 366 age- and sex-matched controls from the same cohort. Using information recorded by school physicians, we performed logistic regression analyses to estimate the relative risks (RR) associated with various genital anomalies. We found the risk for testicular cancer to be raised for men with a history of cryptorchidism [RR = 5.2; 95% confidence interval (CI) = 2.1-13.0], inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7), hypospadias (RR = 4.2; 95% CI = 0.4-42.7), and hydrocele (RR = 2.4; 95% CI = 0.6-9.0). We observed no decrease in the risk associated with cryptorchidism after correction of the maldescent in early childhood. The RR of testicular cancer in the contralateral, normally descended testis in unilateral cryptorchid men was increased to 3,6.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
6) Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. A.J. Swerdlow, 1982 United Kingdom	Case-control study. 87 deaths from testicular cancer in children in Great Britain from 1953 to 1973, while the controls were children who died from other causes.	Inguinal hernia	Association between urogenital abnormalities and testicular cancer	RR = 2.05, p-value >0.05	For inguinal hernia, the relative risk (RR) was 2.05 with a p-value >0.05, indicating no significant risk associated with inguinal hernia. For hydrocele, the RR was 2.99 with a p-value of 0.15, also suggesting no significant risk associated with hydrocele. It is important to note that these results did not show a significant association between these specific genitourinary anomalies and the risk of testicular cancer in children.
7) Sports activities and risk of testicular cancer. A. J. Coldman, 1982 Canada	Case-control study. Men with testicular seminoma (cases) and men without testicular cancer (controls). The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk.	Inguinal hernia	Association between inguinal hernia and risk of testicular cancer	(RR) = 2,86 (IC 95 % : 1,24 - 6,74)	The study examined characteristics of childhood and adolescence in a case-control study of patients treated for testicular seminoma at a regional treatment center between 1970-77. A total of 128 seminoma patients were included, matched with controls diagnosed with skin cancer or Hodgkin's disease. Data collection involved reviewing medical records and obtaining detailed occupational histories. No significant differences were found in sibship size, parental age at subject's birth, infectious diseases, or hormone imbalance conditions. Socio-economic status and urban-rural residence also did not show a relationship with case-control status. The study utilized questionnaires and statistical analyses to investigate potential risk factors associated with testicular seminoma.The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk.The study found a significant association between a history of inguinal hernia and testicular cancer. Patients with testicular seminoma who reported a history of inguinal hernia had a higher risk of developing testicular cancer compared to controls. Even after controlling for cryptorchidism, the overall risk remained elevated. The effect of inguinal hernia varied with age at diagnosis, with those diagnosed before the age of 15 having a much higher risk than those diagnosed after that age. The findings suggest that a history of inguinal hernia, especially occurring at a young age, may be an important risk factor for the subsequent development of testicular cancer. This highlights the significance of considering postnatal risk factors.
8) The epidemiology of testicular cancer in upstate New York . Brenda P. Haughey, 1989. USA	Case-control study. Compared individuals from upstate New York between January 1977 and June 1980 diagnosed with testicular cancer (cases) to individuals without testicular cancer (controls) to identify potential risk factors associated with the disease.	Inguinal hernia	Association Inguinal hernia (risk factors) and testicular cancer	OR = 2.17, (IC 95% : 1.3 - 4.4)	The study on testicular cancer in upstate New York found significant associations between certain factors and testicular cancer risk. Factors such as exposure to high temperatures at work, bathing preference, history of diseases associated with high fever, occupational exposures to fertilizers, phenols, and fumes or smoke, as well as testicular trauma from activities like riding a bicycle or motorcycle, were linked to increased odds of testicular cancer. Specifically, individuals with a history of hernia showed an odds ratio of 2.17 for testicular cancer, indicating a significant association . These findings suggest that both environmental and personal factors may play a role in the development of testicular cancer. The study highlights the importance of considering various exposures and medical histories when assessing the risk of this type of cancer.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
9) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987 United Kingdom.	Case-control study. 259 cases of testicular cancer, 238 men with other diagnoses attending the same radiotherapy centers as the cases, and 251 hospitalized patients not attending radiotherapy services. Two control groups - men with other diagnoses attending the same radiotherapy centers as the cases, and hospitalized patients not attending radiotherapy services.	Inguinal hernia	Association between inguinal hernia, mumps orchitis, infection and testicular cancer	Inguinal Hernia : RR = 1.6 (p = 0.14)	The case-control study on the etiology of testicular cancer conducted by Swerdlow et al. (1987) involved 259 cases of testicular cancer, 238 men with other diagnoses, and 251 hospitalized patients. The study found an increased risk of testicular cancer associated with a history of mumps orchitis (RR = 12.7, p = 0.006) and atopy (RR = 1.8, p = 0.03). Inguinal hernia showed a relative risk of 1.6, although it was not statistically significant. The study did not provide specific relative risk values for other urogenital malformations. The discussion highlighted the challenges in accurately determining past testicular position in cryptorchidism cases and the potential biases in case-control studies related to this issue. Further research, particularly cohort studies, was suggested to provide more reliable data on malignancy risks in cryptorchidism. The association between inguinal hernia and undescended testis was noted, but the extent to which this explains the increased risk of testicular cancer associated with hernia remains unclear. Discussion: The study results underscore the importance of considering factors such as mumps orchitis and atopy in assessing the risk of testicular cancer. The challenges in accurately determining past medical history, especially in cryptorchidism cases, highlight the need for more robust study designs like cohort studies. The discussion also addresses the potential confounding factors related to inguinal hernia and undescended testis.
10) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case-control studies in Denmark. Henrik Møller, 1995 denmark	Case-control study Cases were Men born in Denmark between 1916 and 1970, with testicular cancer diagnosed between 1986 and 1988, frequency-matched controls by year of birth, from the Danish Central Population Register. Cryptorchidism cases identified from two hospital-based case series. Cryptorchidism controls identified from the general population.	Inguinal hernia	Association between inguinal hernia, testicular atrophy and testicular cancer	Inguinal hernia: RR = 1,4, (IC 95% :1,0 - 2,1)	The study conducted in Denmark aimed to investigate the association between cryptorchidism and testicular cancer. Data collection involved contacting men by mail and conducting telephone interviews. Information on cryptorchidism, inguinal hernia, testicular atrophy, and other congenital malformations was gathered. The data were analyzed using contingency tables and logistic regression analysis, with controls frequency-matched to cases by year of birth. The study found associations between testicular cancer and cryptorchidism, as well as testicular atrophy. The relative risk of testicular cancer was higher in men with a history of testicular atrophy. The study also highlighted the importance of early treatment for cryptorchidism and its potential impact on the risk of testicular cancer.The study found that inguinal hernia was weakly associated with testicular cancer overall, with an odds ratio (OR) of 1.4 and a 95% (CI) of 1.0-2.1. However, when the analysis was restricted to reported inguinal hernia in the absence of cryptorchidism or testicular atrophy, the association disappeared . This suggests that the association between inguinal hernia and testicular cancer may be influenced by the presence of other conditions such as cryptorchidism or testicular atrophy. The association with inguinal hernia was much stronger in one of the series compared to the other, indicating potential differences in the study populations. The study also highlighted that the association between inguinal hernia and testicular cancer was not significant once the analysis was adjusted for other conditions, suggesting that the presence of cryptorchidism or testicular atrophy may confound the relationship between inguinal hernia and testicular cancer.
11) Testicular cancer in young men: the search for causes of the epidemic increase in the United States. Linda Morris Brown, 1987. USA	Case-control study. 271 men with testicular cancer and 259 controls in the Washington, DC area. Cases were men aged 18-42 who were newly diagnosed with testicular cancer between January 1976 and June 1981 and were referred to three collaborating medical centers. Controls were selected from the same geographical area.	Inguinal hernia	Association between inguinal hernia, mumps orchitis, infection and testicular cancer	Inguinal Hernia : RR = 1,2 (IC 95%: 0,6-2,7)	The study investigated various factors potentially related to the risk of testicular cancer in young men and aimed to evaluate if any of these factors could explain the significant increases in testicular cancer incidence over time. Factors such as sociodemographic characteristics, childhood residence, religion, and external factors affecting testicular temperature were examined. The study found a slight excess risk for individuals spending their childhood in urban areas compared to rural areas. While there was an apparent excess of Mormons with testicular cancer, it was not statistically significant. External factors like the type of underwear worn or bathing habits did not show significant differences between cases and controls. Additionally, individuals with undescended testis were found to be at an increased risk for developing testicular cancer. However, the association between mumps orchitis and testicular cancer was not statistically significant. Regarding a history of hernia and testicular cancer, the study did not find a substantial risk associated with a history of groin hernia operation. This lack of significant association suggests that a history of hernia may not be a strong risk factor for testicular cancer in the studied population.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
12) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. Tollerud, 1985. USA	Case-control study. Newly diagnosed cases of testicular cancer referred to three participating hospitals from January 1976, through June 1981, and controls with similar characteristics of age, sex, and race selected from individuals with other forms of cancer hospitalized at the same institutions.	Inguinal hernia	Association between family history of urogenital anomalies in close relatives of patients and testicular cancer	SIR:3,9 (IC 95%: 1,7-9)	Focuses on the family history of urogenital anomalies in close relatives of patients with testicular cancer, such as inguinal hernia, cryptorchidism, varicocele, hydrocele, etc. It explores how these family histories may be related to the risk of developing testicular cancer. The study was a case-control study that examined the occurrence of testicular cancer and urogenital anomalies in family members. Six familial clusters with testicular cancer in first-degree relatives were identified. Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis . 6 out of 269 testicular cancer cases (2.2%) had a first-degree relative with testicular cancer, compared to 1 out of 259 controls (0.4%) . Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population . Cryptorchidism was reported in 17% of familial cases, 2.7% of controls, and 5.3% of cases with no family history of testicular cancer . The presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia
17) Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Margaret R. KARAGAS, 1989. USA	Population-based case-control study. Included 323 men with germ cell tumors of the testis diagnosed between 1977 and 1984, as well as 658 selected controls. The comparators in the study were individuals with and without testicular cancer, allowing for the comparison of factors such as intrascrotal temperature elevation and its potential association with the incidence of testicular cancer in noncryptorchid men.	Varicocele	Association between varicocoele and the risk of developing testicular cancer	RR=1,8 (CI 95 %: 0,9 - 3,4)	The study investigated the potential link between elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Here is a summary of the results and discussion: No significant association was found between testicular cancer and wearing tight-fitting underwear or heat-resistant clothing at work. A slightly higher proportion of men with testicular cancer reported wearing long underwear for more than three months per year compared to controls. Controls reported more use of hot tubs or saunas than men with testicular cancer. A slightly higher proportion of men with testicular cancer had a history of physician-diagnosed varicocele. The study did not provide strong support for the hypothesis that intermittent intrascrotal temperature elevation contributes to the development of testicular cancer. Previous research has shown that increased intrascrotal temperature can affect spermatogenesis and sperm morphology. Further evaluation is needed to determine if continuous temperature elevation, such as that seen in varicocele, may increase the risk of testicular cancer. These findings suggest that while there may be some associations between intrascrotal temperature and testicular cancer, more research is required to fully understand the potential mechanisms involved.
24) Is increased body mass index associated with the incidence of testicular germ cell cancer? Dieckmann KP, 2008 Germany	Nationwide multicentric case-control study. Included a total of 8,498 patients with testicular germ cell cancer, compared to 2,070 age-matched male probands from the German National Health Survey.	Obesity	Association between BMI and Obesity and testicular cancer	($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls, for the age group of 18-29 years.	Statistical significance is achieved ($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls" for the age group of 18-29 years. This indicates that in young men aged 18-29 years, there was a statistically significant association between higher BMI categories and testicular germ cell cancer compared to controls. The data on body dimensions, including BMI, were self-reported by the participants. This self-reporting method may introduce bias and inaccuracies in the data, which could affect the reliability of calculating the OR. The study lacked complete data on other potential risk factors for testicular germ cell cancer. Without comprehensive information on all relevant risk factors, calculating a meaningful OR could be challenging and may lead to biased results. Due to the limitations in data quality and completeness, the researchers chose to conduct a descriptive analysis of BMI frequencies instead of calculating the OR, as a more appropriate and feasible approach given the available data Unfortunately, due to the limitations mentioned earlier, a formal calculation of odds ratios was not feasible in this study.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
25) Testis Cancer: Post-Natal Hormonal Factors, Sexual Behaviour and Fertility. A.J. Swerdlow, 1989. United Kingdom	Case-control study. 259 testis cancer cases and 2 sets of controls. Controls were men without testis cancer in the same aera. Study to investigate the relationship between testis cancer risk and variables related to hormonal status, sexual behavior, and fertility.	Obesity	Association between obesity, Height, age of puberty, hormonal status, sexual behavior, fertility, and testicular cancer	RR = 1,83 (IC 95% : 0,83-4,05)	For obesity, the study found that the risk of testis cancer was raised for men with a high Quetelet's index of obesity as adults, but this increase was not statistically significant. The relative risk (RR) for obesity in relation to testis cancer was 1.83 (0.83-4.05). The study did not find a consistent association between testis cancer risk and age at puberty, need to shave, obesity, alcohol intake, animal fat intake, and sexual behavior. There was a significant excess of seminomas in very tall men, but no significant linear trend of risk with height. Testis cancer cases showed lower fertility than controls, but this was mainly due to the higher frequency of cryptorchidism among cases. Among non-cryptorchid subjects, there was no clear evidence of an association between infertility and testis cancer risk. The data and previous literature do not provide convincing evidence that testis cancer risk is related to hormone levels, sexual behavior, or infertility, except in cases of cryptorchidism. Direct measures of hormone levels may be desirable to assess risk more accurately, especially in special groups with hormonal abnormalities. While infertility is unlikely to be a major risk factor for testis cancer, further study is needed to explore the possibility of increased risk among non-cryptorchid infertile men, possibly through a cohort approach.
26) Body size at birth and adulthood and the risk for germ-cell testicular cancer Lorenzo Richiardi, 2003 Sweden	Nested case-control study. 371 patients with testicular cancer, registered in the Swedish Cancer Registry between 1958 and 1996 and aged 20-54 years at diagnosis, and 1238 individually matched controls were identified. Information on adult body size at age 18 years was obtained for all subjects through the Military Service Conscription Register, whereas perinatal information was obtained through birth records at the subjects' respective maternity wards.	Obesity	Association between adult BMI and height, weight and height of birth, and Germ Cell testicular cancer	No association between the risk for testicular cancer and body mass index was found.	Height was positively associated with testicular cancer risk, and the association persisted after taking into account perinatal characteristics. The adjusted odds ratio (OR) was 1.55 [95% confidence interval (CI), 1.10-2.17] for the third tertile of height as compared with the first. Long duration of gestation was negatively associated with testicular cancer risk [OR = 0.64 (95% CI, 0.45-0.91), post-term compared with term], whereas high birth weight appeared to increase the risk [OR = 1.35 (95% CI, 0.99-1.85)]. In conclusion, adult height and perinatal factors acted independently, suggesting that both the fetal life and the childhood and adolescence periods are windows of susceptibility to exposures that influence the risk for testicular cancer.
12) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. TOLLERUD, 1985. USA	Case-control study. Newly diagnosed cases of testicular cancer referred to three participating hospitals from January 1976, through June 1981, and controls with similar characteristics of age, sex, and race selected from individuals with other forms of cancer hospitalized at the same institutions	Hydrocele	Association between a familial history of hydrocele and familial testicular cancer	SIR: 1,3 (IC à 95%: 0,2-8,9)	The study focuses on the family history of urogenital anomalies in close relatives of patients with testicular cancer, such as inguinal hernia, cryptorchidism, varicocele, hydrocele, etc. It explores how these family histories may be related to the risk of developing testicular cancer. The study was a case-control study that examined the occurrence of testicular cancer and urogenital anomalies in family members. Six familial clusters with testicular cancer in first-degree relatives were identified. Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis . 6 out of 269 testicular cancer cases (2.2%) had a first-degree relative with testicular cancer, compared to 1 out of 259 controls (0.4%) . Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population . Cryptorchidism was reported in 17% of familial cases, 2.7% of controls, and 5.3% of cases with no family history of testicular cancer . The presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
5) Genital anomalies and risk for testicular cancer in Danish men. A Prener, 1996. Danemark	Case-control study. 183 cases of testicular cancer registered in the Danish Cancer Registry. For each case, 2 age- and sex-matched controls were selected, resulting in a total of 366 controls. . In a cohort of Danish boys characterized by (1) being born between 1941 and 1957, (2) having attended schools in a defined area of Denmark	Hydrocele	Association between urogenital anomalies and testicular cancer	RR = 2,4 (IC 95 % = 0,6-9,0)	In a cohort of Danish boys characterized by being born between 1941 and 1957, having attended schools in a defined area of Denmark, and having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985. We selected 366 age- and sex-matched controls from the same cohort. Using information recorded by school physicians, we performed logistic regression analyses to estimate the relative risks (RR) associated with various genital anomalies. We found the risk for testicular cancer to be raised for men with a history of cryptorchidism [RR = 5.2; 95% confidence interval (CI) = 2.1-13.0], inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7), hypospadias (RR = 4.2; 95% CI = 0.4-42.7), and hydrocele (RR = 2.4; 95% CI = 0.6-9.0). We observed no decrease in the risk associated with cryptorchidism after correction of the maldescent in early childhood. The RR of testicular cancer in the contralateral, normally descended testis in unilateral cryptorchid men was increased to 3,6.
6) Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. A.J. Swerdlow, 1982. United Kingdom	Case-control study based on 87 deaths from testicular cancer in children in Great Britain from 1953 to 1973. The cases were children who died from testicular cancer, while the controls were children who died from other causes.	Hydrocele	Association between urogenital anomalies and testicular cancer	RR = 2.99 p-value = 0.15	For inguinal hernia, the relative risk (RR) was 2.05 with a p-value >0.05, indicating no significant risk associated with inguinal hernia. For hydrocele, the RR was 2.99 with a p-value of 0.15, also suggesting no significant risk associated with hydrocele. It is important to note that these results did not show a significant association between these specific genitourinary anomalies and the risk of testicular cancer in children.
27) Association between Testicular Cancer and Epididymoorchitis: A Population-Based Case-Control Study. LI-Ting Kao, 2016 China	Population-based case-control study. Included 372 patients with testicular cancer and 3,720 age-matched controls without testicular cancer the Taiwan Longitudinal Health Insurance Database 2005.	Orchitis, epididymitis and genital infection	Association between testicular cancer and prior epididymo-orchitis	OR = 47,17 (IC 95% = 23,83 - 93,40)	The results of the study showed a significant association between testicular cancer and prior epididymoorchitis. OR was 38,24 (95% CI: 19.91–73.46), and after adjusting for potential confounders, the odds ratio remained significant at 47.17 (95% CI: 23.83–93.40) . Additionally, testicular microlithiasis was also found to be significantly associated with testicular cancer, with an adjusted odds ratio of 5.88 (95% CI: 2.77–12.48) . The study highlighted the importance of regular urological examinations for patients with a history of epididymoorchitis and suggested the need for further biological studies to understand the mechanisms underlying this association.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999. United Kingdom	Case-control study. Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas. Each case was matched with a control selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	Orchitis, epididymitis and genital infection	Association between a history of STD and testicular cancer	**for Non seminoma**: OR = 1,8 (CI 95%: 1-3,2)	In this , a history of sexually transmitted diseases (STDs) was associated with an increased risk of non-seminoma compared to pure seminoma tumors. The odds ratio (OR) for the association between a history of STDs and non-seminoma tumors was 1.8 (95% confidence interval [CI]: 1.0-3.2). This suggests that individuals with a history of STDs may have a higher risk of developing non-seminoma testicular germ cell tumors compared to those with pure seminoma tumors.
28) Mumps, orchitis and testicular germ cell tumors: A cause for concern? Trabert B. 2011. USA	Case-control Study. TGCT cases diagnosed between 2002 and 2005 (n = 767) were matched on age, race and serum draw date to at least one control (n = 929).	Orchitis, epididymitis and genital infection	Association between mumps, orchitis and testicular cancer	For TGCT : Orchitis OR= 2.17 [95% CI: 1.37-3.46], Mumps [OR: 0.88, 95% CI: 0.63-1.23]. For Seminoma : Orchitis [OR: 1.65, 95% CI: 0.94-2.90], Mumps [OR: 0.79, 95% CI: 0.52-1.20]. For Non seminoma : Orchitis OR 2.50 [95% CI: 1.43-4.38], Mumps [OR: 1.22, 95% CI: 0.81-1.84].	Orchitis was associated with a 2.17-fold increased risk of TGCT [95% CI: 1.37-3.46], while mumps did not show a significant association with TGCT risk [OR: 0.88, 95% CI: 0.63-1.23]. For seminoma, neither mumps [OR: 0.79, 95% CI: 0.52-1.20] nor orchitis [OR: 1.65, 95% CI: 0.94-2.90] were identified as risk factors. In the case of nonseminoma, orchitis was associated with a 2.50-fold increased risk [95% CI: 1.43-4.38], while mumps did not show a significant association [OR: 1.22, 95% CI: 0.81-1.84]. These findings suggest a potential link between orchitis and TGCT risk, particularly in the nonseminoma subgroup.
9) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987. United Kingdom	Case-control study. 259 cases of testicular cancer, two control groups, 238 men with other diagnoses attending the same radiotherapy centers as the cases, and 251 hospitalized patients not attending radiotherapy services.	Orchitis, epididymitis and genital infection	Association between inguinal hernia, mumps orchitis, infection and testicular cancer	Mumps orchitis : RR = 12.7 (p = 0.006)	The study found an increased risk of testicular cancer associated with a history of mumps orchitis (RR = 12.7, p = 0.006) and atrophy (RR = 1.8, p = 0.03). Discussion: The study results underscore the importance of considering factors such as mumps orchitis and atrophy in assessing the risk of testicular cancer. The challenges in accurately determining past medical history, especially in cryptorchidism cases, highlight the need for more robust study designs like cohort studies. The discussion also addresses the potential confounding factors related to inguinal hernia and undescended testis, emphasizing the need for further research to elucidate the mechanisms underlying the observed associations.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
29) Childhood infections, orchitis and testicular germ cell tumours. Trabert B, 2012. USA	Case-control Study. 97 cases, and 194 Controls were drawn from the same well-defined population.	Orchitis, epididymitis and genital infection	relationship between common infections and TGCT risk	OR of 1.80 (95% CI: 0.74 – 4.42)	For mumps: Odds ratio (OR) was 1.03 (95% CI: 0.89 – 1.20), indicating no significant association with TGCT risk. The analysis showed very little heterogeneity among theresults, with an I2 value of 6.1% (indicating low heterogeneity). For mumps orchitis or orchitis: The random-effects model produced a pooled OR of 1.80 (95% CI: 0.74 – 4.42) for the association with TGCT risk. There was considerable heterogeneity across study-specific ORs, with an I2 value of 69.0% (suggesting high heterogeneity). Sensitivity analyses indicated that two recent studies contributed most to the heterogeneity. When these studies were removed, the heterogeneity decreased significantly (I2 = 0.0%) and the pooled ORs for fixed- and random-effects models became more consistent. These results suggest that while mumps did not show a significant association with TGCT risk, mumps orchitis or orchitis had a more varied impact across studies, with some studies indicating an increased risk.
11) Testicular cancer in young men: the search for causes of the epidemic increase in the United States. Linda Morris Brown, 1987. USA	Case-control study. Included 271 men with testicular cancer and 259 controls in the Washington, DC area. Cases were men aged 18-42 who were newly diagnosed with testicular cancer between January 1976 and June 1981 and were referred to three collaborating medical centers in the Washington, DC area. Controls were selected from the same geographical area. as the cases, allowing for the comparison of various factors between the two groups to assess potential associations with testicular cancer risk.	Orchitis, epididymitis and genital infection	Association between a history of mumps orchitis, orchitis and testicular malignancies	Mumps Orchitis RR = 5,8 (IC 95%: 0,7-129,7)	The study investigated various factors potentially related to the risk of testicular cancer in young men and aimed to evaluate if any of these factors could explain the significant increases in testicular cancer incidence over time. Factors such as sociodemographic characteristics, childhood residence, religion, and external factors affecting testicular temperature were examined. The study found a slight excess risk for individuals spending their childhood in urban areas compared to rural areas. While there was an apparent excess of Mormons with testicular cancer, it was not statistically significant. External factors like the type of underwear worn or bathing habits did not show significant differences between cases and controls. Additionally, individuals with undescended testis were found to be at an increased risk for developing testicular cancer. However, the association between mumps orchitis and testicular cancer was not statistically significant. Overall, the study did not find clear associations between these factors and the risk of testicular cancer, highlighting the complexity of potential risk factors for this type of cancer . The study used a case-control design to assess the associations between various factors and testicular cancer risk. Factors like undescended testis and groin hernia were explored, with undescended testis showing a significantly elevated risk for testicular cancer. Other medical conditions and histories like mumps orchitis, allergies, and specific treatments were also examined, with varying levels of association with testicular cancer risk. The study did not find significant associations between testicular cancer risk and factors like specific allergies or bathing habits. These findings contribute to the understanding of potential risk factors for testicular cancer in young men. For mumps orchitis and testicular cancer, the study reported a positive but non-significant association, with mumps orchitis being reported for six cases and one control. However, the method of questioning subjects about a history of mumps and potential recall bias, as well as the difficulty in distinguishing mumps orchitis from other testicular conditions, may have influenced the results.

Tables 3 : Cohort studies (12 studies).

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
13) Congenital anomalies in children with testicular germ cell tumor. Shiego Sakashita, 1980. Japan	Retrospective cohort study. Compared cases of testicular germ cell tumors in children who had undergone orchiectomy at the hospital. Children with testicular germ cell tumors who had congenital anomalies. Comparator was the total cohort.	Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	Inguinal hernia estimated incidence of 10% among children with testicular tumor.	The identified abnormalities included a retrocaval ureter, diverticulum of the bladder, Down's syndrome, and an ipsilateral inguinal hernia. In the study, it was observed that among the 25 children with testicular germ cell tumors, 4 patients (16%) had associated congenital malformations. Among these anomalies, inguinal hernia was the most common, with an estimated incidence of 10% among children with testicular tumors. The results suggest that there may be a link between tumor development and the presence of congenital anomalies in children with testicular tumors. Therefore, it is recommended to carefully examine young patients with testicular tumors for potential congenital abnormalities The study highlighted the differences in etiology, pathology, and clinical features of pediatric testicular germ cell tumors compared to adult cases. The predominant tumors in children were teratomas and yolk sac tumors, with a better prognosis in children than in adults. The study suggested that the oncogenesis of testicular tumors in infants may begin in utero.
14) Familial Testicular Cancer in a Single-centre Population. D.J.A. Sonneveld, 1999. Netherlands	Retrospective cohort study in a single-center population. The study population consisted of patients with testicular cancer and their affected first-degree, second-degree, or third-degree relatives. Cases compared to non-familial cases.	Inguinal hernia	Association between urogenital anomalies and testicular cancer	Prevalence of a history of inguinal hernia: 3 patients (8.3%) among familial testicular cancer. Do not mention a specific calculation of relative risk or other measures of association to assess the link between inguinal hernia and testicular cancer.	The study retrospectively analyzed familial testicular cancer cases in a single-center population of 693 patients treated between 1977 and 1997. It aimed to assess the proportion of familial testicular cancer cases and estimate the relative risk for first-degree relatives of patients. Additionally, the study evaluated the occurrence of bilateral testicular neoplasms and urogenital developmental anomalies in families with a predisposition to testicular cancer. The results showed that 3.5% of patients had a first-degree relative with testicular cancer, with a total of 24 familial cases belonging to 17 families. Regarding inguinal hernia, 3 patients (8.3%) with familial testicular cancer had a history of inguinal hernia. In familial cases with affected first-degree relatives, inguinal hernias were present in 8% of cases. The study found that the proportion of urogenital developmental anomalies, such as undescended testis (UDT) and inguinal hernias, was slightly higher in familial testicular cancer cases compared to historical general testicular cancer cases. The presence of UDT in 17% of testicular cancer cases with affected second- or third-degree relatives suggests an association between UDT and familial occurrence of testicular cancer. It is noted that there may be bias in ascertainment due to over-reporting of relatives with these anomalies.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
15) Occurrence of testicular cancer in patients operated on for cryptorchidism and inguinal hernia. Pinczowski, 1991 Sweden	Retrospective cohort study. 2 population-based cohorts comprising 2,918 men who underwent an operation for a cryptorchid testis and 30,199 who underwent surgery for an inguinal hernia. Comparator was the total cohort.	Inguinal hernia	Association between inguinal hernia and testicular cancer	RR = 1,1 (95% CI: 0,4-2,2)	Studied the incidence of testicular cancer in 2 population-based cohorts comprising 2,918 men who underwent an operation for a cryptorchid testis and 30,199 who underwent surgery for an inguinal hernia. Complete followup during the 19-year period was achieved by record linkage to the National Swedish Cancer Registry. In the cryptorchidism cohort 4 cases of testicular cancer occurred versus 0.54 expected, yielding a relative risk of 7.4 (95% confidence interval 2.0 to 19.0). Of these patients 3 had undergone a bilateral operation due to intra-abdominal testes. There was no evidence of an association between inguinal hernia and risk of testicular cancer (relative risk = 1.1, 95% confidence interval 0.4 to 2.2). The validity of data was further supported by relative risk estimates close to unity in a comparison group of appendectomy patients. They conclude that patients with a cryptorchid testis experience a substantially increased relative risk of testicular cancer. However, the low absolute risk, 4 cases during 25,360 person-years of observation, does not appear to justify special surveillance after an operation for an undescended testis.
16) The Relation Between Testicular Tumours, Undescended Testes, and Inguinal Hernias. Th. Wobbes, 1980 USA	Retrospective cohort study. 230 patients with malignant testicular tumors to investigate the relationship between undescended testes, inguinal hernias, and testicular malignancies. Comparator was the total cohort.	Inguinal hernia	association between inguinal hernia and risk of testicular cancer	Unknown	An inguinal hernia was found in 3.4% of the patients with a testicular tumour. This is in agreement with the normal incidence of inguinal hernia [Mustard et al, 19691 Consequently, there seems to be no increased risk for patients with a history of an operai:ion for inguinal hernia. But this contradicts Morrison [1967] , who calculated 2.9 times as high a risk of malignant testicular tumour. In the study, it was reported that the risk of malignancy in an undescended testis proved to be about 17 times greater than in the normal population. Regarding inguinal hernia, no increased risk was found for patients with a history of inguinal hernia.
18) Varicocoele in adolescence and testicular cancer in young adulthood. Guy Verhovsky, 2022. Israel	Nationwide, population-based, historical cohort study. Included 1,521,661 Israeli male adolescents with a mean age of 17.5 years who were screened for varicocoele during the years 1967–2012. Comparators were adolescents with varicocoele stages 2 and 3 to those without varicocoele in terms of the incidence of testicular cancer during young adulthood.	Varicocele	Association between varicocoele in adolescence and the risk of developing testicular cancer in young adulthood	RR: 0,816 (IC 95% : 0,615 - 1,083)	Elevated intrascrotal temperature has been suggested as a risk factor for testicular cancer. Varicocele was linked to increased intrascrotal temperature, but whether it is associated with testicular cancer is unclear. 1,521,661 Israeli male adolecents (mean age 17.5 ± 0.4 years), were screened for varicocele as part of their medical assessment prior to compulsory military service during the years 1967-2012. The diagnosis of testicular cancer was ascertained from linkage of records to the Israeli National Cancer Registry. In total, 53,210 adolescents were diagnosed with varicocele prior to military service. Of 1,988 (0.13% of the total cohort) men who were diagnosed with testicular cancer, 54 (0.1%) had varicocele prior to military service and 1934 were not exposed to the elevated intrascrotal temperature resulting from varicocele, p=0.314. The age at cancer diagnosis and the distribution of seminomas vs. non-seminomas did not differ significantly between those with and without varicocele in adolescence. Varicocele was also not associated with testicular cancer, in a multivariable analysis controlling for sociodemographic factors. Varicocele in adolecents was not found to be associated with testicular cancer in young adults.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
19) Worldwide Distribution, Risk Factors, and Temporal Trends of Testicular Cancer Incidence and Mortality: A Global Analysis. Huang J, 2022. International	Epidemiological Study.	obesity	Association between obesity, cholesterol and Testicular Cancer	Not available	There was a wide variation in the testicular cancer burden with the highest mortality found in low-income countries, and the regions of Central America and South America, while the highest incidence was observed in high-income countries, especially in Western and Northern Europe. They found a positive association for HDI, GDP, alcohol drinking, inactivity, overweight, obesity, and hypercholesterolaemia with testicular cancer incidence, while a negative correlation was observed between GDP and mortality of testicular cancer. Globally, testicular cancer incidence had been increasing particularly in the younger population, although its deaths rates had been decreasing. Socioeconomic indices, alcohol drinking, inactivity, overweight, obesity, and high plasma lipid levels are associated with testicular cancer incidence and mortality.
20) Regional variations in testicular cancer rates in Ireland.M. Alsinnawi, 2010. ireland	Epidemiological study. Analyze the incidence of testicular cancer in different counties of Ireland and explore potential risk factors. The population includes individuals diagnosed with testicular cancer in various counties of Ireland between January 1994 and December 2007.	Obesity	Association between adolescent obesity rates and testicular cancer rates	The distribution of obesity among adolescents in different regions of Ireland did not align with the regional variations in testicular cancer rates.	Aimed to investigate the incidence of testicular cancer in different counties of Ireland between 1994 and 2007. The study compares the rates of testicular cancer in Cork County to those in other counties, such as Galway and Meath, to identify significant variations in incidence. The study also explored potential factors such as cryptorchidism, socio-economic status, environmental pollutants, and teenage obesity as risk factors for the development of testicular cancer.Cork County had a significantly higher rate of testicular cancer compared to other counties in Ireland.While high rates of cryptorchidism were observed in Cork, they alone could not explain the elevated incidence of testicular cancer.Areas with higher socio-economic status in Cork showed significantly higher rates of testicular cancer.Organic pollutants linked to testicular cancer were identified in industries located only in Cork.Teenage obesity rates in Cork were not higher than in other regions.The study did not find a significant association between obesity and testicular cancer incidence. The distribution of obesity among adolescents in different regions of Ireland did not align with the regional variations in testicular cancer rates. This suggests that factors other than obesity may play a more significant role in explaining the observed differences in testicular cancer incidence across counties.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
21) Body size and cancer of the testis. T.W.Davies, 1990. Denmark	Retroscpective population-based cohort study. 438 cases of testicular cancer and three controls for each case. The data originated from health examinations of men liable for military service in Denmark. The study compared body measurements (height, weight, and body mass index). Comparator was the general population of Danemark.	Obesity	Association between BMI and obesity and testicular cancer	BMI >25 <19 years old : RR=0,7 (IC 95%: 0,3-1,3) >19 years old : RR=0,8 (IC 95%: 0,4-1,8)	The study found no systematic statistically significant differences in body measurements between cases and controls. The study did not confirm the initial hypothesis that high fat or calorie intake leading to relative obesity could be a promotional factor for testicular cancer. Instead, the findings indicated a trend where men who later developed testicular cancer were lighter, smaller, and thinner than unaffected controls, particularly in the younger age group. The difference between cases and controls diminished with increasing age, suggesting that weight gain during adolescence might be a promotional factor for testicular cancer. Additionally, the study noted that the social class distribution of testicular cancer cases in Denmark did not align with findings from other studies associating testicular cancer with higher social class, suggesting potential environmental and lifestyle factors at play in different populations.
22) The impact of height and body mass index on the risk of testicular cancer in 600,000 Norwegian men. Tone Bjørge, 2006. Norway	Cohort study. Population consisted of 600,000 Norwegian men, including 557,043 adults and 111,543 adolescents, who were eligible for the study after excluding individuals with a prior diagnosis of testicular cancer. The Comparators was the total cohort.	Obesity	Association between BMI and height, and testicular cancer	**<u>Adults:</u> for seminomas:** RR = 1.07 (95% CI: 1.00-1.19) **for non-seminomas:** RR=1.00 (95% CI: 0.90-1.00) **for all testicular cancer cases:** RR = 0.66 (95% CI: 0.48-0.90) **<u>Adolescents:</u>** **for seminomas:** RR = 1.00 (95% CI: 0.81-1.00) **for non-seminomas:** RR = 0.88 (95% CI: 0.76-1.03) **for all testicular cancer cases:** RR = 1.00 (95% CI: 0.76-1.00)	The study examined the impact of height and body mass index (BMI) on the risk of testicular cancer in 600,000 Norwegian men. The findings indicated that there was a significant association between height and the risk of testicular cancer, with taller men having a higher risk. Additionally, the study found a U-shaped relationship between BMI and testicular cancer risk, with both underweight and obese men showing an increased risk compared to men with normal BMI. The findings supported previous research indicating a positive association between height and testicular cancer risk. The U-shaped relationship between BMI and testicular cancer risk was also emphasized, with underweight and obese men showing increased risks, suggests that both underweight and obese individuals may have an increased risk of developing testicular cancer compared to individuals with a normal BMI.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results	Comments
23) Visceral abdominal obesity – is there an increased prevalence in men presenting with testicular teratoma? Lee Grant, 2010. United Kingdom	Retrospective cohort study. 22 male patients who had undergone staging CT between 2004 and 2007 for testicular teratoma. Comparators were 22 male patients matched for age, sex, and body mass index, selected from patients who had a normal CT examination following an acute episode of renal colic.	Obesity	Association between visceral abdominal obesity and testicular teratoma	RR = 1,56 (CI: 1,08-2,2)	The study investigated the association between visceral abdominal obesity and testicular teratoma in male patients. The researchers compared abdominal adipose tissue distribution in 22 patients with testicular teratoma to 22 control patients matched for age, sex, and body mass index. They found that patients with testicular teratoma had a significantly higher ratio of visceral to subcutaneous adipose tissue volumes compared to the control group, with the ratio being 1.56 times greater in teratoma patients. This suggests that individuals with testicular teratoma have a relatively greater proportion of abdominal visceral adipose tissue. The findings support the association between increased visceral adiposity and testicular teratoma. The authors suggested that the metabolic activity of visceral adipose tissue may play a role in the development of testicular teratoma.
30) Incidence of testicular malignancies and correlation to risk factors in a TESE population of subfertile men. Banz-Jansen, 2011. Germany	Retrospective Cohort study: 302 patient files of subfertile men who underwent testicular biopsies for TESE procedures between January 1995 and December 2004.	Orchitis, epididymitis and genital infection	Association between a history of mumps orchitis and testicular cancer	Mumps orchitis occurred among 20% of patients with testicular tumors .	Main objective of the study was to evaluate the incidence of testicular malignancies and risk factors in the subfertile male population treated with TESE in Northern Germany. These results suggest a potential association between a history of mumps orchitis and testicular malignancies in the studied population, but statistical results were not precised, and not significant.
31) Mumps orchitis and testicular tumours. W. Ehrengut, 1977. Germany	Retrospective cohort study Population: Patients with testicular tumors in Hamburg, comparator was the total cohort population.	Orchitis, epididymitis and genital infection	Association between a history of mumps orchitis, orchitis and testicular cancer	Not precised	The study focused on patients with testicular tumors and their history of mumps orchitis and epididymitis. The findings revealed a low occurrence of mumps orchitis in the past medical history of patients with testicular neoplasms. However, a significant proportion of patients with testicular tumors had a history of epididymitis on the affected side, suggesting a potential association. The study did not find any cases of testicular tumors among patients previously treated for mumps orchitis.

Only significant results are summarized following extraction data from 14 studies, and ranked by heat exposures (Table 4).

Table 4 : Only significant results.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results
1) Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia, Linda M. Pottern, 1985.	Case-control study. Included 271 cases of testicular cancer and 259 controls,men aged 18-42 years, all referred to three collaborating medical centers in the Washington, DC, area, to assess the relative risk associated with a history of undescended testis and hernia repair.	Cryptorchidism	Association between increased temperatur e related to cryptorchidism and testicular cancer	RR=3,7 (CI 95% : 1,6-8,6)
		Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	Inguinal Hernia treated after 7 years old: RR = 6,1 (CI 95% : 1-43,9)
2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999.	Case-control study. Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas. Controls were selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	Inguinal hernia	Association Inguinal hernia (risk factors) and testicular cancer	Inguinal hernia (all): for other histological types of tumors: OR = 2.39 (95% CI: 1,28-4,46). Inguinal hernias diagnosed before the age of 15: for pure seminoma : OR = 3.12 (95% CI: 1,42-6,88) for other histologies : OR = 2.49 (95% CI: 1,06-5,88)
3) Congenital malformations and testicular germ cell tumors, Britton Trabert, 2013.	Population-based case-control study. Included individuals diagnosed with testicular germ cell tumors (cases) and matched controls without the tumors.	Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	OR =1,37 (CI 95%: 1,11-1,68)
4) Cryptorchidism, hernia, and cancer of the testis. Alan S. Morrison, 1976.	Case-control Study. 596 patients with testicular cancer and 602 unaffected controls, who had served in the U.S. military between 1950 and 1970, were studied based on the medical histories and military records of the participants.	Inguinal hernia	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	RR: 2,9 (CI 95%: 1,3-7,0)
7) Sports activities and risk of testicular cancer. A. J. Coldman, 1982	Case-control study. Men with testicular seminoma (cases) and men without testicular cancer (controls). The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk.	Inguinal hernia	association between inguinal hernia and risk of testicular cancer	(RR) = 2,86 (CI 95 % : 1,24 - 6,74)
8) The epidemiology of testicular cancer in upstate New York . Brenda P. Haughey, 1989.	Case-control study. Compared individuals from upstate New York between January 1977 and June 1980 diagnosed with testicular cancer (cases) to individuals without testicular cancer (controls) to identify potential risk factors associated with the disease.	Inguinal hernia	Association Inguinal hernia (risk factors) and testicular cancer	OR = 2.17, (CI 95% : 1,3 - 4,4)
10) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case-control studies in Denmark. Henrik Møller, 1995	Case-control study Cases were Men born in Denmark between 1916 and 1970, with testicular cancer diagnosed between 1986 and 1988, frequency-matched controls by year of birth, from the Danish Central Population Register. Cryptorchidism cases identified from two hospital-based case series. Cryptorchidism controls identified from the general population.	Inguinal hernia	Association between inguinal hernia, testicular atrophy and testicular cancer.	Inguinal hernia: RR = 1,4, (CI 95% : 1,0 - 2,1)
12) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. Tollerud, 1985.	Case-control study. Newly diagnosed cases of testicular cancer referred to three participating hospitals from January 1976, through June 1981, and controls with similar characteristics of age, sex, and race selected from individuals with other forms of cancer hospitalized at the same institutions.	Inguinal hernia	Association between family history of urogenital anomalies in close relatives of patients and testicular cancer.	SIR = 3,9 (CI 95% : 1,7-9)
24) Is increased body mass index associated with the incidence of testicular germ cell cancer? Dieckmann KP, 2008	Nationwide multicentric case-control study. Included a total of 8,498 patients with testicular germ cell cancer, compared to 2,070 age-matched male probands from the German National Health Survey.	Obesity	Association between BMI and Obesity and testicular cancer	($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls, for the age group of 18-29 years.

Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Heat Exposure and OC	Main outcome results
22) The impact of height and body mass index on the risk of testicular cancer in 600,000 Norwegian men. Tone Bjørge, 2006.	Cohort study. Population consisted of 600,000 Norwegian men, including 557,043 adults and 111,543 adolescents, who were eligible for the study after excluding individuals with a prior diagnosis of testicular cancer. The Comparators was the total cohort.	Obesity	Association between BMI and height, and testicular cancer	For seminomas: RR = 1.07 (95% CI: 1,00-1,19)
23) Visceral abdominal obesity – is there an increased prevalence in menpresenting with testicular teratoma? Lee Grant, 2010.	Retrospective cohort study. 22 male patients who had undergone staging CT between 2004 and 2007 for testicular teratoma. Comparators were 22 male patients matched for age, sex, and body mass index, selected from patients who had a normal CT examination following an acute episode of renal colic.	Obesity	Association between Visceral abdominal obesity and testicular teratoma	RR = 1,56 (CI: 1,08-2,2)
27) Association between Testicular Cancer and Epididymoorchitis: A Population-Based Case-Control Study. LI-Ting Kao, 2016	Population-based case-control study. Included 372 patients with testicular cancer and 3,720 age-matched controls without testicular cancer the Taiwan Longitudinal Health Insurance Database 2005.	Orchitis, epididymitis and genital infection	Association between testicular cancer and prior epididymoorchitis.	OR = 47,17 (CI 95% = 23,83 - 93,40)
2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999.	Case-control study. Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas. Each case was matched with a control selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	Orchitis, epididymitis and genital infection	Association between a history of STD and testicular cancer	for Non seminoma: OR = 1,8 (CI 95%: 1-3,2)
28) Mumps, orchitis and testicular germ cell tumors: A cause for concern? Trabert B. 2011.	Case-control Study. TGCT cases diagnosed between 2002 and 2005 (n = 767) were matched on age, race and serum draw date to at least one control (n = 929).	Orchitis, epididymitis and genital infection	Association between mumps, orchitis and testicular cancer (seminoma, non seminoma and TGCT)	For TGCT : Orchitis OR= 2.17 [95% CI: 1.37-3.46]. For Non seminoma : Orchitis OR 2.50 [95% CI: 1.43-4.38]
9) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987.	Case-control study. 259 cases of testicular cancer, 238 men with other diagnoses attending the same radiotherapy centers as the cases, and 251 hospitalized patients not attending radiotherapy services. Two control groups - men with other diagnoses attending the same radiotherapy centers as the cases, and hospitalized patients not attending radiotherapy services.	Orchitis, epididymitis and genital infection	Association between inguinal hernia, mumps orchitis, infection and testicular cancer.	Mumps orchitis : RR = 12.7 (p = 0.006)

3. NARRATIVE ANALYSIS (QUALITATIVE ANALYSIS) BY STUDY TYPE: ONLY SIGNIFICANT RESULTS.

- **CRYPTORCHIDISM:**

As stated earlier, the association between cryptorchidism and testicular cancer has been the subject of several studies, reviews, and meta-analyses. Unfortunately, during our research, we were unable to find any study specifically highlighting the association between scrotal heat caused by cryptorchidism and testicular cancer, or the pathophysiological role of cryptorchidism in the development of testicular cancer. However, the study « Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia » by Linda M. Pattern, without providing statistical results for this main outcome, found a significant association between cryptorchidism and testicular cancer, and seems to suggest, without statistical link, the hypothesis of scrotal heat as factor favouring the carcinogenesis of testicular tumours.

We therefore thought it relevant to put the analysis of another study, "Clinical and biological characteristics of infertile men with a history of cryptorchidism" by R. Mieusset, into perspective, and will elaborate the parallel qualitative analysis of these results during the discussion. (144,145)

- **INGUINAL HERNIA:**

1) Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia. Linda M. Pottern, 1985.

This large case-control study was carried out involving 271 cases of testicular cancer and 259 controls, conducted in the Washington, DC area, aimed to investigate the relationship between cryptorchidism, inguinal hernia, and the risk of testicular cancer in young men aged 18-42. Testicular cancer cases diagnosed between 1976 and 1981 were compared with controls diagnosed with cancers other than genital tract cancer during the same period. Subjects were selected from three collaborating medical centers, and detailed information was obtained through interviews and medical records. The study found a higher risk of testicular cancer in men with a history of undescended testes, especially if the condition was not corrected. Additionally, men who underwent hernia surgery after age 7 had an elevated risk of testicular cancer on the same side as the hernia. The study found that there was no substantial excess risk of testicular cancer for men without cryptorchidism who had undergone hernia repair. However, for those who had hernia repair at older ages (28 years and above), there was an elevated risk of testicular cancer on the same side as the hernia. This elevated risk was particularly notable for bilateral hernia repairs. The study suggests that this increased risk may be due to delayed correction of undescended testes or other factors related to late hernia repair. The study highlighted that while previous research had shown a relationship between inguinal hernia and testicular cancer risk, the association was not well-defined.

The study proposed several explanations for this finding, including the possibility of chance, the impact of late correction of undescended testes among individuals with both hernia and cryptorchidism, or the potential risk elevation due to delayed correction. The study supported the importance of early surgical correction of cryptorchidism and inguinal hernia to reduce the risk of testicular cancer.

2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999.

This Case-control Study, explores associations with testicular tumour risk, including factors like undescended testis, age at puberty, and exercise habits. The study investigated the association between risk factors and testicular germ cell tumors by histological tumor type.

The analysis by histological tumour type reveals significant differences in risk factors, providing insights into the aetiology of different tumour types. The study used unconditional logistic regression to estimate odds ratios and identify risks that differed significantly by tumour type. The findings of this study suggest that the relationship between inguinal hernias and testicular cancer risk may vary depending on the histological tumor type. The OR for inguinal hernia were similar for pure seminoma and other tumours, however, when subdivided by age at diagnosis of hernia. Risks were raised, and of similar magnitude, for hernias diagnosed before the age of 15, whilst for hernias diagnosed later than this the risk was increased for non-seminoma tumours (OR = 2.3), but reduced (no significant) for pure seminomas (OR = 0.6). The risk associated with hernias diagnosed after the age of 15 was no significant, and higher for non-seminoma tumours than for pure seminoma. Indeed, the risks associated with inguinal hernias were similar overall for both histological groups, but analysis by age at hernia diagnosis revealed different risk patterns.

3) Congenital malformations and testicular germ cell tumors. Britton Trabert, 2013.

This case-control study was conducted in Sweden using population-based registry data. It aimed to investigate the association between congenital malformations and testicular germ cell tumors (TGCT). A total of 7,552 TGCT cases diagnosed between 1964 and 2008 were included, along with 32,955 controls matched for year and county of birth. Hospitalization records were used to identify congenital malformations, and statistical analysis was performed using conditional logistic regression. The study found that hypospadias, inguinal hernia, and other genital malformations were associated with an increased risk of TGCT, supporting the hypothesis that prenatal exposures affecting proper genital development may be related to the development of these tumors. The results showed that cryptorchidism was associated with an increased risk of TGCT with an OR of 3.18 (95% CI: 2.50-4.04), hypospadias with an OR of 2.41 (95% CI: 1.27-4.57), inguinal hernia with an OR of 1.37 (95% CI: 1.11-1.68), and other genital malformations with an OR of 2.19 (95% CI: 1.17-4.10). These results highlight significant associations between these genital malformations and the risk of testicular germ cell tumors (TGCT). The study found that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, are associated with an increased risk of testicular germ cell tumors (TGCT). Specifically focusing on inguinal hernia, the analysis revealed that there is an elevated risk of TGCT associated with inguinal hernia, even after accounting for the association

between cryptorchidism and TGCT. This suggests that inguinal hernia may independently contribute to the risk of developing testicular cancer. In the discussion, the study highlighted that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, were linked to an increased risk of testicular germ cell tumors (TGCT), supporting the notion that prenatal exposures affecting proper genital development may play a role in TGCT etiology. The findings also suggested that the associations between these abnormalities and TGCT risk may represent distinct etiologic pathways, with inguinal hernia showing consistent increased risks across various studies. Additionally, the study discussed the potential implications of early diagnosis of malformations, such as hypospadias, on the severity of defects and their relation to TGCT risk.

4) Cryptorchidism, hernia, and cancer of the testis. Alan S. Morrison, 1976.

This study focused on young adults serving in the Army, and the data collection process ensured that information on undescended testis and other exposures was obtained consistently for cases and controls. The risk ratio estimated for testicular cancer associated with undescended testis was 8.8, with previous studies suggesting a risk ratio closer to 10. The study found that men with a history of undescended testis had a significantly higher risk of testicular cancer, with a risk ratio estimate of 8.8. Additionally, individuals who had undergone hernia operation before age 15 were 2.9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed. Furthermore, undescended testis was closely associated with the side of the testicular tumor, with tumors often occurring in the testis that had been undescended. Histologically, tumors in patients with undescended testis were more likely to be seminomas compared to other types of tumors. The data suggested a moderate elevation of risk among subjects with repaired hernias, indicating a potential link between inguinal hernia and testicular cancer risk. Further research is warranted to explore the relationship between inguinal hernia and the risk of testicular cancer in more detail. The discussion highlighted three peaks in testicular cancer morbidity and mortality: at 2 years of age, early adulthood, and old age. The study also discussed the potential causal relationship between undescended testis and testicular cancer, emphasizing the need for further research, especially regarding the impact of surgical correction of undescended testis on testicular cancer rates. The study found a significant association between undescended testis and an increased risk of testicular cancer, with a risk ratio estimate of 8.8. Individuals who had undergone hernia operation before age 15 were 2.9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed, and hernia was not associated with tumors of a specific histologic type. The discussion emphasized the peaks in testicular cancer morbidity and mortality at different ages and highlighted the need for further research to explore the causal relationship between undescended testis, hernia, and testicular cancer.

7) Sports activities and risk of testicular cancer. A. J. Coldman, 1982.

This study examined characteristics of childhood and adolescence in a case-control study of patients treated for testicular seminoma at a regional treatment center between 1970-77. A total of 128 seminoma patients were included, matched with controls diagnosed with skin cancer or Hodgkin's disease. Data collection involved reviewing medical records and obtaining detailed occupational histories. No significant differences were found in sibship size, parental age at subject's birth, infectious diseases, or hormone imbalance conditions. Socio-economic status and urban-rural residence also did not show a relationship with case-control status. The study utilized questionnaires and statistical analyses to investigate potential risk factors associated with testicular seminoma. The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk. The study found a significant association between a history of inguinal hernia and testicular cancer, (RR) = 2,86 (IC 95 %: 1,24 - 6,74). Patients with testicular seminoma who reported a history of inguinal hernia had a higher risk of developing testicular cancer compared to controls. Even after controlling for cryptorchidism, the overall risk remained elevated. The effect of inguinal hernia varied with age at diagnosis, with those diagnosed before the age of 15 having a much higher risk than those diagnosed after that age. The findings suggest that a history of inguinal hernia, especially occurring at a young age, may be an important risk factor for the subsequent development of testicular cancer. This highlights the significance of considering postnatal risk factors, such as inguinal hernia, in assessing the risk of testicular cancer. Further research is warranted to explore the underlying mechanisms linking inguinal hernia to testicular cancer and to better understand the implications of this association for cancer prevention and early detection strategies.

8) The epidemiology of testicular cancer in upstate New York. Brenda P. Haughey, 1989.

The study on testicular cancer in upstate New York found significant associations between certain factors and testicular cancer risk. Factors such as exposure to high temperatures at work, bathing preference, history of diseases associated with high fever, occupational exposures to fertilizers, phenols, and fumes or smoke, as well as testicular trauma from activities like riding a bicycle or motorcycle, were linked to increased odds of testicular cancer. Specifically, individuals with a history of hernia showed an odds ratio of 2.17 (CI 95%: 1.3 - 4.4) for testicular cancer, indicating a significant association. These findings suggest that both environmental and personal factors may play a role in the development of testicular cancer. The study highlights the importance of considering various exposures and medical histories when assessing the risk of this type of cancer. Further research and awareness of these risk factors could aid in early detection and prevention strategies for testicular cancer.

10) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case-control studies in Denmark. Henrik Møller, 1995.

This study conducted in Denmark aimed to investigate the association between cryptorchidism and testicular cancer. Here is a summary of how the study was conducted: The study included four groups of men: Testicular cancer cases identified through the Danish Cancer Registry. Controls matched by year of birth to the testicular cancer cases from the Danish Central

Population Register. Cryptorchidism cases identified from two hospital-based case series. Cryptorchidism controls identified from the general population. Data collection involved contacting men by mail and conducting telephone interviews. Information on cryptorchidism, inguinal hernia, testicular atrophy, and other congenital malformations was gathered. The data were analyzed using contingency tables and logistic regression analysis, with controls frequency-matched to cases by year of birth. The study found associations between testicular cancer and cryptorchidism, as well as testicular atrophy. The relative risk of testicular cancer was higher in men with a history of testicular atrophy. The study also highlighted the importance of early treatment for cryptorchidism and its potential impact on the risk of testicular cancer. The study found that inguinal hernia was weakly associated with testicular cancer overall, with an odds ratio (OR) of 1.4 and a 95% confidence interval (CI) of 1.0-2.1. However, when the analysis was restricted to reported inguinal hernia in the absence of cryptorchidism or testicular atrophy, the association disappeared. This suggests that the association between inguinal hernia and testicular cancer may be influenced by the presence of other conditions such as cryptorchidism or testicular atrophy.

12) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. Tollerud, 1985.

This case-control examined the occurrence of testicular cancer and urogenital anomalies in family members. It focuses on the family history of urogenital anomalies in close relatives of patients with testicular cancer, such as inguinal hernia, cryptorchidism, varicocele, hydrocele. They explore how these family histories may be related to the risk of developing testicular cancer, and examined the occurrence of testicular cancer and urogenital anomalies in family members. Six familial clusters with testicular cancer in first-degree relatives were identified. Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis. 6 out of 269 testicular cancer cases (2.2%) had a first-degree relative with testicular cancer, compared to 1 out of 259 controls (0.4%). The several clusters of genitourinary malformations in families of men with testicular cancer, although the data collected on this is insufficient for formal analysis, add to previous evidence suggesting that familial associations of testicular cancer and such malformations may sometimes have a genetic basis. The high prevalence of cryptorchidism, inguinal hernias, and hydroceles among men in these families suggests that an underlying alteration in urogenital embryogenesis may be associated with the familial predisposition to testicular neoplasia. Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population. Cryptorchidism was reported in 17% of familial cases, 2.7% of controls, and 5.3% of cases with no family history of testicular cancer. The presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia.

- **VARICOCELE:**

Regarding the association between varicocele and testicular cancer, unfortunately, both included studies, did not find any significant results. (98,146)

- **OBESITY:**

22) The impact of height and body mass index on the risk of testicular cancer in 600,000 Norwegian men. Tone Bjørge, 2006.

The study examined the impact of height and body mass index (BMI) on the risk of testicular cancer in 600,000 Norwegian men. The findings indicated that there was a significant association between height and the risk of testicular cancer, with taller men having a higher risk. Additionally, the study found a U-shaped relationship between BMI and testicular cancer risk, with both underweight and obese men showing an increased risk compared to men with normal BMI. These results suggest that both height and BMI may play a role in the development of testicular cancer in men. The study highlighted the importance of considering both height and BMI as potential risk factors for testicular cancer. The findings supported previous research indicating a positive association between height and testicular cancer risk. The U-shaped relationship between BMI and testicular cancer risk was also emphasized, with underweight and obese men showing increased risks, suggests that both underweight and obese individuals may have an increased risk of developing testicular cancer compared to individuals with a normal BMI. This non-linear relationship indicates that extreme values of BMI, both low and high, may be associated with higher risks of testicular cancer. The study suggested that these factors may reflect underlying biological mechanisms related to cancer development. Additionally, the study discussed the implications of these findings for future research and the potential for interventions targeting modifiable risk factors such as BMI.

23) Visceral abdominal obesity – is there an increased prevalence in men presenting with testicular teratoma? Lee Grant, 2010.

The study investigated the association between visceral abdominal obesity and testicular teratoma in male patients. The researchers compared abdominal adipose tissue distribution in 22 patients with testicular teratoma to 22 control patients matched for age, sex, and body mass index. The researchers compared the ratio of visceral to subcutaneous adipose tissue volumes between these two groups to assess the association between visceral abdominal obesity and testicular teratoma. They found that patients with testicular teratoma had a significantly higher ratio of visceral to subcutaneous adipose tissue volumes compared to the control group, with the ratio being 1.56 times greater in teratoma patients. This suggests that individuals with testicular teratoma have a relatively greater proportion of abdominal visceral adipose tissue. The study acknowledged limitations such as its retrospective design, the assumption of no confounding metabolic conditions, and the lack of baseline imaging for assessing changes in fat distribution with tumor presentation. Despite these limitations, the findings support the association between increased visceral adiposity and testicular teratoma. The authors suggested that the metabolic activity of visceral adipose tissue may play a role in the development of testicular teratoma. In conclusion, the study demonstrated a link between visceral abdominal obesity and testicular teratoma, highlighting the potential impact of adipose tissue distribution on cancer risk. Further research is needed to explore the underlying mechanisms and potential implications for cancer prevention and management.

24) Is increased body mass index associated with the incidence of testicular germ cell cancer? Dieckmann KP, 2008.

Statistical significance is achieved ($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls" for the age group of 18-29 years. This indicates that in young men aged 18-29 years, there was a statistically significant association between higher BMI categories and testicular germ cell cancer compared to controls. The data on body dimensions, including BMI, were self-reported by the participants. This self-reporting method may introduce bias and inaccuracies in the data, which could affect the reliability of calculating the OR. The study lacked complete data on other potential risk factors for testicular germ cell cancer. Without comprehensive information on all relevant risk factors, calculating a meaningful OR could be challenging and may lead to biased results. Unfortunately, due to the limitations mentioned earlier, a formal calculation of odds ratios was not feasible in this study.

- **HYDROCELE:**

Regarding the association between hydrocele and testicular cancer, unfortunately, the 3 included studies, did not find any significant results. (147–149)

- **URO-GENITAL INFECTIONS, ORCHITIS, AND EPIDIDYMITIS:**

2) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999.

This Case-control study, involved Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas. Each case was matched with a control selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year, a history of sexually transmitted diseases (STDs) was associated with an increased risk of non-seminoma compared to pure seminoma tumors. The odds ratio (OR) for the association between a history of STDs and non-seminoma tumors was 1.8 (95% confidence interval [CI]: 1.0-3.2). There was an increased risk of non-seminoma (OR = 2.93) compared with pure seminoma (OR = 1.55) associated with ever having had a sexually transmitted disease ($p = 0.018$). This suggests that individuals with a history of STDs may have a higher risk of developing non-seminoma testicular germ cell tumors compared to those with pure seminoma tumors.

9) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987.

This case-control study on the etiology of testicular cancer involved 259 cases of testicular cancer, 238 men with other diagnoses, and 251 hospitalized patients. The study found an increased risk of testicular cancer associated with a history of mumps orchitis (RR = 12.7, $p = 0.006$) and atopy (RR = 1.8, $p = 0.03$). Inguinal hernia showed a relative risk of 1.6, although it was not statistically significant. An increased odds ratio for seminoma (OR = 3.8) was associated with childhood herniorrhaphy before age 15, whereas no association was found with nonseminoma tumours. The study did not provide specific relative risk values for other urogenital malformations and highlighted the challenges in accurately determining past testicular position in cryptorchidism cases and the potential biases in case-control studies related to this issue. Further research, particularly cohort studies, was suggested to provide more

reliable data on malignancy risks in cryptorchidism. The association between inguinal hernia and undescended testis was noted, but the extent to which this explains the increased risk of testicular cancer associated with hernia remains unclear. The study results underscore the importance of considering factors such as mumps orchitis and atrophy in assessing the risk of testicular cancer. The challenges in accurately determining past medical history, especially in cryptorchidism cases, highlight the need for more robust study designs like cohort studies. The discussion also addresses the potential confounding factors related to inguinal hernia and undescended testis, emphasizing the need for further research to elucidate the mechanisms underlying the observed associations.

27) Association between Testicular Cancer and Epididymo-orchitis: A Population-Based Case-Control Study. LI-Ting Kao, 2016.

Population-based case-control study. The study population included 372 patients with testicular cancer and 3,720 age-matched controls without testicular cancer. The comparator was from from the Taiwan Longitudinal Health Insurance Database 2005. The results of the study showed a significant association between testicular cancer and prior epididymo-orchitis. The crude odds ratio for this association was 38.24 (95% CI: 19.91–73.46), and after adjusting for potential confounders, the odds ratio remained significant at 47.17 (95% CI: 23.83–93.40). Additionally, testicular microlithiasis was also found to be significantly associated with testicular cancer, with an adjusted odds ratio of 5.88 (95% CI: 2.77–12.48). The study highlighted the importance of regular urological examinations for patients with a history of epididymo-orchitis and suggested the need for further biological studies to understand the mechanisms underlying this association.

28) Mumps, orchitis and testicular germ cell tumors: A cause for concern? Trabert B. 2011.

In this Case-control Study. TGCT cases diagnosed between 2002 and 2005 (n = 767) were matched on age, race and serum draw date to at least one control (n = 929). Orchitis was associated with a 2.17-fold increased risk of TGCT [95% CI: 1.37-3.46], while mumps did not show a significant association with TGCT risk [OR: 0.88, 95% CI: 0.63-1.23]. For seminoma, neither mumps [OR: 0.79, 95% CI: 0.52-1.20] nor orchitis [OR: 1.65, 95% CI: 0.94-2.90] were identified as risk factors. In the case of nonseminoma, orchitis was associated with a 2.50-fold increased risk [95% CI: 1.43-4.38], while mumps did not show a significant association [OR: 1.22, 95% CI : 0.81-1.84]. These findings suggest a potential link between orchitis and TGCT risk, particularly in the nonseminoma subgroup.

4. 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 case-control studies: 4 had a score of 5/9, and 15 had a score of 7/9 or higher.

- For non-randomized cohorts: 1 article had a score of 5/9, 4 had a score of 6/9, and 7 had a score of 7/9 or higher.

It shows a good overall quality of the selected studies with a total of 22 studies with a score of 7/9 or higher.

Table 5: Bias assessment of case-control studies.

Article	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 (blind status)	Same method of ascertainment for case and controls	Non-Response rate (maximum 5% difference)	Total
1	*	*	*	*	**		*		7
2	*	*	*	*	**	*	*		8
3	*	*	*	*			*		5
4	*	*	*	*	**	*	*		8
5	*	*	*	*	**		*		7
6	*	*	*	*			*		5
7	*	*	*	*	**		*		7
8	*	*	*	*	**		*		7
9	*	*	*	*	**	*	*		8
10	*	*	*	*	**		*		7
11	*	*	*	*	**		*	*	8
12	*	*	*	*	**		*		7
17	*	*	*	*	**		*		7
24	*	*	*	*	**		*		7
25	*	*	*	*	**		*		7
26	*	*	*	*			*		5
27	*	*	*	*	**		*		7
28	*	*	*	*			*		5
29	*	*	*	*	**		*		7

Table 6 : Bias assessment of non-randomized cohorts

Article	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
13	*	*	*		**	*	*		7
14	*	*	*	*		*	*		6
15	*	*	*	*		*	*		6
16	*	*	*	*		*		*	6
18	*	*	*	*	**		*	*	8
21	*	*	*	*		*	*	*	7
22	*		*	*	**	*	*	*	8
23	*	*	*	*	**	*	*		8
19	*	*		*			*		4
20	*		*	*	**	*	*	*	8
30	*	*	*	*	**	*	*		8
31	*	*	*	*		*	*		6

D. DISCUSSION

This study aimed to elucidate the relationship between intra-testicular exposure to supra physiological temperatures and an increased testicular cancer risk. It shows a positive correlation between three intra-scrotal exposures of endogenous heat and testicular cancer for inguinal hernia, obesity and prior uro-genital infections, particularly for certain histological types. (144,147,150–161) However, no significant association was found for varicocele or hydrocele. (147–149,162,163)

This large-scale study, conducted after a rigorous screening of 2588 articles, stands on robust methodology, due to its adherence to PRISMA guidelines with a double-blind selection strategy, and the overall quality of the final selected studies using the NOS bias assessment tool (22 studies with a score of 7/9 or higher). Plus, the results of this study can easily be extrapolated to the general population thanks to the use of only healthy men from the general population as an external comparator, enhancing its external validity.

Studying testicular heat in its relationship with carcinogenesis also suggests a better definition of testis temperature elevation; which is one of the limits of our study. To limit this measurement bias, before starting the study we made a non-systematic review of what kind of heat exposure could have real impact on either sperm parameters, or a significant impact on body temperature (references in the introductory part). Finally, 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”, 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.

This study was concerned only with intra-corporeal causes of testicular heat and cannot be applied to exogenous causes such as clothing, external hot sources and occupational heat exposures. Dr Carton's literature review showed that there may be a link between external heat exposures to only high temperatures (represented by the metal industry) and testicular cancer.

The correlation between cryptorchidism and testicular cancer is firmly established on robust scientific foundations, exemplified by Pottern and al. work. (144) Their study revealed a sixfold higher risk of testicular cancer in the cryptorchid testis compared to the contralateral one among individuals with unilateral cryptorchidism, with a direct relationship observed between the age of corrective surgery and cancer risk. These findings have significantly influenced clinical practice in urology, advocating for corrective orchidopexy surgery to be performed before the age of 3 years. (50,86,164)

Regarding inguinal hernia, 8 studies identified a significant association between this condition and testicular cancer, indicating a risk increase ranging from 1.37 to 2.3 in the odds ratio. (144,147,150–155)

For inguinal hernias diagnosed after age 15, the risk was not significant, increased for non-seminoma tumours but reduced for seminomatous tumors. (150)

The findings of studies suggest that the relationship between inguinal hernias and testicular cancer risk may vary depending on the histological tumor type.

Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis. Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population. Indeed, the presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia. (147,153,154)

Futhermore in the Moller and Al. study, it was noted that the association with inguinal hernia was much stronger in one of the series compared to the other, indicating potential differences in the study populations. The study also highlighted that the association between inguinal hernia and testicular cancer was not significant once the analysis was adjusted for other conditions, suggesting that the presence of cryptorchidism or testicular atrophy may confound the relationship between inguinal hernia and testicular cancer. (155)

Overall, various results suggest that while there may be a weak association between inguinal hernia and testicular cancer, this association is influenced by an underlying alteration in urogenital embryogenesis, and the presence of other conditions such as cryptorchidism or testicular atrophy. (147,151,152,154,165) Further research is needed to explore the complex interplay of various confounding risk factors contributing to testicular cancer development.

Three studies have demonstrated a significant association between obesity and testicular cancer. (156–158) Bjørge and al. proposed a non-linear relationship, suggesting a U-shaped curve with an increased risk observed at both extremes of BMI. Dieckmann and al. found a significant association among younger patients with a BMI ranging from 25 to 30 kg/m2. Lerro et al. reported controversial findings, suggesting an inverse relationship with a potentially protective role of increased BMI in testicular cancer. (166) Moreover, in various studies, the distribution of obesity among men did not align with the regional variations in testicular cancer rates. This suggests that factors other than obesity may play a more significant role in explaining the observed differences in testicular cancer incidence. (167–169) Given the limitations in these conflicting studies, including the predominant reliance on self-reported data by participants and the lack of analysis on other potential risk factors, further investigation is warranted.

As for prior urogenital infections, testicular cancer seemed to be positively associated with orchitis (150,161), epididymitis (160), mumps orchitis (159), and sexual transmitted diseases. (150) The relation between infections and testicular cancer relies mostly on the response to chronic inflammation which is involved in several different steps leading to carcinogenesis.

Hydrocele and varicocele have not demonstrated a significant association with the risk of testicular cancer. (147–149,162,163) The studies available were limited in number and sample

size, potentially lacking statistical power to establish a meaningful correlation. This underscores the challenge of demonstrating a relevant relationship due to insufficient data and statistical strength.

Another limit of this study, and certainly the major one, is confounding bias. Since most studies have focused on uro-genital anomalies in general, and since genital pathologies are often syndromic, many of the significant results associated these different pathologies and factors with testicular cancer, making it difficult to distinguish them individually in the analyses, and inducing a significant confounding bias.

While this approach enhances the statistical power and significance of their findings, it complicates the nuanced understanding of testicular carcinogenesis on a pathology-specific level and induces a significant confounding bias. However, it corroborates the notion that all these conditions increasing intrinsic testicular heat are crucial to investigate in testicular carcinogenesis. Therefore, future studies should focus on each individual criteria to further elucidate the strength of association with testicular cancer risk.

Moreover, the pathogenicity of testicular heat with these pathologies in their relationship with testicular cancer remains unclear. Although no study has demonstrated a direct link between heat in for example cryptorchidism (most analysed pathology) and testicular cancer, some studies have indicated a deleterious effect of this condition on testicular exocrine functions. (170–172) For instance, Mieusset et al. reported an increased prevalence of cryptorchidism among infertile men, with 45% of infertile men with a history of cryptorchidism exhibiting abnormal testicular heat. Additionally, they observed a higher spermatic alteration in men with a history of cryptorchidism and increased testicular heat compared to those with normal heat levels. (173)

Despite the acknowledged association between heat and testicular function, it remains unclear whether the elevated testicular heat is a consequence of cryptorchidism or occurs independently.

Current hypotheses could be based on a decrease in blood flow in the testis, histological and cellular alterations, and even epigenetic factors. (170,171,174)

Mieusset and al. study suggests that heat may not directly cause cryptorchidism, as elevated temperatures could be a result of testicular atrophy rather than the cause. However, it's noted that Dr. Mieusset's involvement in the development of the "contraceptive slip" introduces a potential conflict of interest. Similarly, Zorgniotti and al. study also suggests that temperature elevation could result from testicular atrophy, potentially due to decreased blood flow and parenchymal tissue. (175,176)

Which accreditated the work of where the hypothesis related to the elevated temperature of the undescended testis with testicular cancer is by inhibiting the differentiation of spermatogonia and resulting in an arrest of spermatogenesis, germ cell depletion, and fibrosis. (174) In addition, the altered position of the testis could alter the function of the somatic cells forming the niche for spermatogonial stem cells' self-renewal and differentiation. The histological

dysgenetic changes in testicles with cancer may be due to abnormalities in the fetal development of germ cells. Testicular germ cell cancer is presumed to derive from carcinoma in situ (CIS) cells that originate from primordial germ cells escaping normal differentiation during fetal development. These CIS cells are considered the precursor of all types of germ cell tumors, except spermatocytoma. Therefore, the dysgenetic changes observed in the histology of testicles in patients with testicular cancer could result from these cellular developmental alterations during the fetal period. (174,177)

Moreover, recent evidence suggests that allelic variants in genes implicated in the development of the testes could be present in a patient with cryptorchidism. In particular, KIT gene variants might be the determinants in the association between this condition and testicular cancer. (178) However, even if an irrefutable higher risk of testicular cancer in patients affected by previous or current cryptorchidism has been found, the real pathogenetic mechanism underlying this association is still unclear. (179)

Regarding scrotal heat exposure, it can also play a role in the histological changes observed in testicles with cancer. Studies have demonstrated that exposure to high temperatures, such as those induced by cryptorchidism or other conditions increasing scrotal heat, can negatively impact spermatogenesis and germ cell health, thereby elevating the risk of testicular cancer. (75,141,180) Thus, in addition to fetal developmental cellular alterations, scrotal heat seems to also contribute to the histological changes seen in testicles associated with testicular cancer.(39,128)

Furthermore, elucidating the underlying pathophysiological mechanisms linking endogenous testicular heat to carcinogenesis warrants concerted research efforts, encompassing molecular, cellular, histological and epidemiological perspectives.

Finally in extrapolating the study as to the safety of male thermal contraception, Dr Rogier's literature review showed that Thermal Male Contraception might be effective for a majority of men, reversible and acceptable for users. However, they raise some concerns about safety, new trial and prospective cohort therefore seem necessary.

E. CONCLUSION AND PERSPECTIVES :

Our study cannot conclude that there is a link between internal heat exposures and testicular cancer because of significant confounding bias and the heterogeneity of results.

With the narrative analysis, we can hypothesis that there may be a link between testicular cancer and intra-scrotal and endogenous source of heat (inguinal hernia, obesity, and prior uro-genital infections), inguinal hernia and obesity being contraindications to the use of thermal contraception. However, regarding the factors of obesity and urogenital infections, these results should be interpreted with caution in the light of the influence of other conditions and associated factors, and the conclusions of new, more recent meta-analyses.

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V. ANNEXES :

Inclusion criteria	Exclusion criteria
- Population: Human, men, and boy, regardless of age - Exposition: 2 One or more supposed elevation of testicular temperature, Internal source of Heat, Intra scrotal source of heat, Testicular and scrotal diseases known to increase testicular temperature: cryptorchidism, inguinal hernia, varicocele, obesity,hydrocele, orchitis, studying body temperature - Primary Outcome: 1 Studies that talk about the main outcome (testicular cancer occurrence) “Testicular Cancer” as an outcome (OR as a statistic result). - Secondary Outcome: Studies that talk about one of the secondary outcomes (MTC’s safety, efficiency, reversibility, acceptability, minimal exposition duration to the occurrence of testicular cancer identified in the included studies, minimal threshold of heat intensity). - Studies: All Clinical trial (retrospective studies, cohort, case-controls, cross-sectionnal studies, case reports, epidemiologic studies) epidemiologic studies, case-controls, cross-sectionnal studies, case reports)	Population: Female, girl, not human, not men, animals Intervention: External addition of heat, external source of heat or about male thermal contraception (other dedicated questions) Studies: Other language than French or English, not an original paper (paper reporting datas of another study), Narrative publication.

Mots clés/Key words :

Concepts	French free terms	English free terms	MeSH terms
Testicule	Testicule / Testiculaire / Scrotum / Génital / Bourse	Testis / Testicle / Testicular / Scrotum / Scrotal / Genital	Testis
Cancer	Cancer / Cancéreux / Tumeur / Néoplasme / Malin / Seminome / Modification cellulaire	Cancer /Cancerous / Tumor / Neoplasm / Malignant / Seminoma / Cellular modification / Malignancy	Neoplasms
Chaleur	Température / Chaud / Chaleur / Hyperthermie	Temperature / Hot / Heat / Heating / Hyperthermia	Hot temperature/ hyperthermia
Contraception	Contraception / Contraceptif / Contrôle des naissances / Contrôle de la fécondité / Moyen / Méthode / Inhibition de la fertilité / Planification familiale	Contraception / Contraceptive / Birth control / Fertility control / Contraceptive device / Contraceptive Method / Fertilization inhibition / Family planning	Contraception
Masculin	Masculin / Homme / Hommes / Mâle	Masculine / Man / Men / Male	Male
Exposition interne	Interne / Intrinsèque / Intérieur / Intra corporelle/ (Chaleur corporelle/)	Internal / Intern / Inside / Intra corporeal / Body Heat/	Intra corporeal Cryptorchidism/ Undescended

	Cryptorchidie / Ectopie testiculaire / Testicule non descendu/ Varicocèle / Hydrocèle testiculaire/ Hydrocèle scrotale/ Hernie inguinale /	Cryptorchidism / Undescended testis / Cryptorchid / Cryptorchid men / Varicocele / Hydrocele testicular/ Inguinal hernia /	testis/ Undescended testes Varicocele / Hydrocele, scrotal/ Hydrocele, testicular Inguinal, hernia
Exposition externe	Externe / Environnement / Environnemental / Professionnel / Ouvrier / Employé Construction / Bâtiment Industrie / Industriel / Fonderie / Fondeur / Verrier / Soudeur Agriculture / Soleil Transport / Chauffeur Textile / Teinturerie / Blanchisserie Alimentation / Restaurant / Boulangerie / Boulanger / Cuisinier / Four Pompier / Feu Spa / Hammam / Bain / Vêtements / Pantalon / Sous-vêtements / Couche / Ordinateur	External / Environment / Environmental / Professional / Occupational / Work / Worker / Employee / Clerk Construction / Constructional / Building Industry / Industrial / Foundry / Foundry / Glassmaker / Welder Agriculture / Agricultural / Farming / Sun Transport / Transportation / Driver Textile / Dyeing / Laundry Bakery / Baker / Cook / Oven / Firefighter / Fire Spa / Hammam / Bath / Hot tub / Clothing / Pants / Underpants / Diaper / Nappy / Laptop	Technology, Industry and Agriculture Occupational groups Clothing

Méthode Thermique	Chaleur / Température scrotale / suspension testiculaire / Slip remonte-testicule / Anneau / Androswitch	Thermal / Thermal method / Thermal devices / Temperature / Thermoregulation / Body temperature / Scrotal temperature / Hyperthermia	0

Equations de recherche/ Searchqueries :

Databases	Search Queries	Results
PUBMED	((testicular neoplasm[MeSH Terms]) OR (testicular cancer[Title/Abstract]) OR (testicular malignancy[Title/Abstract]) OR (scrotal cancer*[Title/Abstract]) OR (scrotal neoplasm*[Title/Abstract])) AND ((cryptorchid*[Title/Abstract]) OR (varicocel*[Title/Abstract]) OR (varicocoel*[Title/Abstract]) OR (inguinal hernia[Title/Abstract]) OR (testicular hydrocele[Title/Abstract]) OR (orchitis[Title/Abstract]) OR (genital infection [Title/Abstract]) OR (weight[Title/Abstract])) (BMI[Title/Abstract]) OR (obesity[Title/Abstract]) (extreme heat [Title/Abstract]) OR (hot[Title/Abstract]) OR (heat*[Title/Abstract]) OR (temperature[Title/Abstract]) OR (hypertherm*[Title/Abstract])) NOT ((orchidopex*[Title/Abstract]) OR (ultrasound*[Title/Abstract]) OR (high frequenc*[Title/Abstract]) OR (sonograph*[Title/Abstract]) OR (radiation*[Title/Abstract]) OR (varicocele/therapy[MeSH Terms]) OR (inguinal, hernia/therapy[MeSH Terms]) OR (testicular hydrocele/therapy[MeSH Terms]) OR (treatment*[Title/Abstract]) OR (therap*[Title/Abstract]) OR (stem cell therapy[Title/Abstract]) OR (metastas*[Title/Abstract]) OR (occupation*[Title/Abstract]) OR (foundr*[Title/Abstract]) OR (weld*[Title/Abstract]) OR (driver*[Title/Abstract]) OR (baker*[Title/Abstract]) OR (glass-mak*[Title/Abstract]) OR (dyer*[Title/Abstract]) OR (laundr*[Title/Abstract]) OR (mine*[Title/Abstract]) OR (blast furnace*[Title/Abstract]) OR (clothing[MeSH Terms]) OR	986 522

	(cloth*[Title/Abstract]) OR (pant*[Title/Abstract]) OR (napp*[Title/Abstract]) OR (pad[Title/Abstract]) OR (sauna[Title/Abstract]) OR (bath*[Title/Abstract]) OR (hammam[Title/Abstract]) OR (hot tub[Title/Abstract]) OR (laptop*[Title/Abstract]) OR (Toxic Actions[MeSH Terms]) OR (Genetic Phenomena[MeSH Terms]) OR (skin neoplasms[MeSH Terms]) OR (firefight*[Title/Abstract]) OR (worker*[Title/Abstract]))	
EMBASE	('testis tumor'/exp OR 'testis tumor' OR 'testicular cancer':ab,ti OR 'testicular neoplasm':ab,ti OR 'testicular malignancy':ab,ti OR 'scrotal cancer':ab,ti OR 'scrotal neoplasm':ab,ti) AND ('cryptorchid*':ab,ti OR 'cryptorchism'/exp OR 'cryptorchism' OR 'varicocele':ab,ti OR 'varicocele'/exp OR 'varicocele' OR 'varicocoele':ab,ti OR 'inguinal hernia'/exp OR 'inguinal hernia' OR 'inguinal hernia':ab,ti OR 'hydrocele':ab,ti OR 'hydrocele'/exp OR 'hydrocele' OR 'extreme heat':ab,ti OR 'high temperature':ab,ti OR 'high temperature'/exp OR 'high temperature' OR 'heat':ab,ti OR 'heating':ab,ti OR 'hyperthermia':ab,ti) NOT ('orchidopexy'/exp OR 'orchidopexy' OR 'orchidopexy':ab,ti OR 'ultrasound':ab,ti OR 'ultrasound'/exp OR 'ultrasound' OR 'high frequency electrotherapy':ab,ti OR 'high frequency ultrasound':ab,ti OR 'sonographer':ab,ti OR 'radiation':ab,ti OR 'radiation'/exp OR 'radiation' OR 'therapy'/exp OR 'therapy' OR 'therapy':ab,ti OR 'treatment outcome':ab,ti OR 'treatment outcome'/exp OR 'treatment outcome' OR 'metastasis'/exp OR 'metastasis' OR 'metastasis':ab,ti OR 'occupation':ab,ti OR 'occupation'/exp OR 'occupation' OR 'foundry':ab,ti OR 'foundry'/exp OR 'foundry' OR 'welding':ab,ti OR 'welding'/exp OR 'welding' OR 'driver':ab,ti OR 'driver'/exp OR 'driver' OR 'baker':ab,ti OR 'dye':ab,ti OR 'laundry':ab,ti OR 'miner':ab,ti OR 'furnace':ab,ti OR 'clothing'/exp OR 'clothing' OR 'clothing':ab,ti OR 'pant*':ab,ti OR 'napp*':ab,ti OR 'sauna':ab,ti OR 'bath':ab,ti OR 'bath'/exp OR 'bath' OR 'hot tub':ab,ti OR 'laptop':ab,ti OR 'laptop'/exp OR 'laptop' OR 'toxic substance'/exp OR 'toxic substance' OR 'toxic substance':ab,ti OR 'toxicity':ab,ti OR 'toxicity'/exp OR 'toxicity' OR 'heredity':ab,ti OR 'heredity'/exp OR 'heredity' OR 'skin tumor'/exp OR 'skin tumor' OR 'skin tumor':ab,ti OR 'fire fighter'/exp OR 'fire fighter' OR 'fire fighter':ab,ti OR 'worker':ab,ti OR 'worker'/exp OR	931

	'worker' OR 'fertility':ti OR 'infertility':ti OR 'fertile':ti OR 'infertile':ti)	
COCHRANE	(Testicular neoplasm OR Testicular Cancer OR Testicular Tumor OR Testicular Seminoma) 681 AND (Cryptorchidism OR Undescended testis OR Cryptorchid OR Varicocele OR Scrotal Varicocele OR Inguinal, hernia OR Hydrocele scrotal OR Hydrocele testicular) OR (heat OR temperature OR hot OR heating OR hyperthermia)	107
LiSSa	((Tumeur Testiculaire) OU (Tumeur des testicules)) ET ((chaleur) OU (Température) OU (cryptorchidie) OU (Varicocèle) OU (Hernie Inguinale) OU (Hydrocèle)((Cancer testiculaire)) ET ((Chaleur) OU (Température) OU (Cryptorchidie) OU (Hydrocèle scrotale) ou (Varicocèle) Ou (Hernie Inguinale) OU (Surpoids) Ou (Obésité) OU (Orchite) OU (infection génitale))	11
CisMEF	Tumeur Testiculaire ou Tumeur des testicules ET Cryptorchidie OU Varicocèle OU Hernie Inguinale OU Hydrocèle OU Chaleur Ou Température élevée OU Cancer testiculaire)) ET ((OU (Température) OU (Cryptorchidie) OU (Hydrocèle scrotale) ou (Varicocèle) Ou (Hernie Inguinale) OU (Surpoids) Ou (Obésité) OU (Orchite) OU (infection génitale))	96
SUDOC (mots dans le texte et titre)	((Cancer testiculaire)) ET ((Chaleur) OU (Température) OU (Cryptorchidie) OU (Hydrocèle scrotale) ou (Varicocèle) Ou (Hernie Inguinale) OU (Surpoids) Ou (Obésité) OU (Orchite) OU (infection génitale) Livres: 3, Thèses version de soutenance: 13, Filtres ajoutés pour exclusion de: Sons, Musique, Partitions, Matériel audio-visuel, Cartes.	18

GOOGLE SCHOLAR	English all in title: **32** All articles with Testicular cancer Articles with at least: cryptorchid OR hydrocele OR varicocele OR hernia OR heat OR temperature OR hyperthermia OR obesity OR orchitis OR inflammation NOT antigens antigen treatment therapy occupation worker bakery baker laundry nappies driver drive glassmaker mines miner foundry welding laptop clothes shock protein ultrasound French: **5** Articles contenant Cancer testicule Articles contenant au moins: cryptorchidie OU varicocèle OU hernie inguinale hydrocèle OU chaleur OU température OU obésité OU surpoids OU inflammation OU orchite NOT profession professionnels professionnel sauna couches soudeur boulanger pompier couches vêtement métier thérapie traitement gène	37
Web Of Science	(TS=(testicular neoplasms) OR TS=(testicular cancer) OR TS=(testicular tumor) OR TS=(scrotal cancer) OR TS=(testicular malignancy)) AND ((TS=(cryptorchidism) OR TS=(varicocele) OR TS=(inguinal hernia) OR TS=(testicular, hydrocele) OR TS=(heat) OR TS=(temperature) OR TS=(hot) OR TS=(heating) OR TS=(hyperthermia)OR TS=(obesity) OR TS= (BMI) OR TS=(orchitis) OR TS= infection)) NOT ((TS=(therapy) OR TS=(orchidopexy) OR TS=(endocrine disruptors) OR TS=(ultrasound) OR TS=(microlithiasis) OR TS=(trauma) OR TS=(Traumatism) OR TS=(heat shock) OR TS=(chemotherapy) OR TS=(surgery) OR TS=(self examination)))	866

Annexe cryptorchidie

Study type	Title. Main author. Publication Year.	Study Type. Comparators.	Heat exposure	Country	Lien O/N	Heat Exposure and OC	Main outcome results	CCL O/N	Comments
Cohorte Rétrospective: Discussion	Does Intratubular Germ Cell Neoplasia, Unclassified Type Exist in Prepubertal, Cryptorchid Testes? Rong Fan and Thomas M. Ulbright. 2012	Retrospective cohort Study.	Cryptorchidism	USA	No	Association between prior intra tubular cell neoplasie and testicular cancer. (no scrotal temperature linked)	/	/	
Cohorte Rétrospective: Discussion	Correction of cryptorchidism and testicular cancer. Hack, W.W.; Sijstermans, K.; van der Voort-Doedens, L.M. 2011	Retrospective cohort Study.	Cryptorchidism	Danemark	No	Association between age of orchydopexy and testicular cancer (no scrotal temperature linked)	/	/	
Case-control, Wrong exposition, Discussion	Association between testicular dysgenesis syndrome (TDS) and testicular neoplasia: Evidence from 20 adult patients with signs of maldevelopment of the testis. NIELS E. SKAKKEBÆK, METTE HOLM, CHRISTINA HOEI-HANSEN, NIELS JØRGENSEN and EWA RAJPERT-DE MEYTS. 2003	Case-control Study.	Cryptorchidism	Danemark	No	Association between TDS (cryptorchidism) and testicular cancer (no scrotal temperature linked)	/	/	
Case-control	1) Andrology: Clinical and biological characteristics of infertile men with a history of cryptorchidism. R. Mieusset, L. Bujan, G. Massat, A. Mansat, F. Pontonnier, 1995.	Case-control Study. The study included 95 men with a history of cryptorchidism who were seeking fertility evaluation and treatment at the center. These men were compared to a fertile population of 85 men who either requested vasectomy or were potential sperm donors. The average age of the men with cryptorchidism was 31.8 years, with a mean duration of infertility of 37.3 months. Secondary infertility was found in 14.7% of the cryptorchid men. The fertile population had an average age of 33.4 years	Cryptorchidism	France	Non	Association between cryptorchidism, intra scrotal temperature and fertility	/	/	For retractile testes and high location of testes based on abnormally high scrotal temperatures: Right retractile testis: OR = 1.51 (95% CI: 0.48-4.73) Left retractile testis: OR = 1.32 (95% CI: 0.43-4.03) High location of testis on the right: OR = 2.50 (95% CI: 0.83-7.84) High location of testis on the left: OR = 3.81 (95% CI: 1.09-15.06) .The study found that 45% of infertile men with a history of cryptorchidism had abnormally high scrotal temperatures, which was associated with more severely impaired spermatogenesis and a higher incidence of primary infertility compared to infertile men with normal scrotal temperatures. Additionally, a retractile testis was more frequently found on the cryptorchid side in infertile men, and this was associated with lower sperm output. Scrotal hyperthermia in cryptorchid infertile men was linked to smaller testicular volumes and lower sperm production compared to those with normal scrotal temperatures .
Cohort Study. Wrong OC: Discussion.	Clinical and histopathological results of the adult patients with unilateral cryptorchidism. Ates, F; Soydan, H; Okcelik, S; Cirakoglu, A; Yilmaz, I; Malkoc, E; Karademir, K; 2016.	Cohort Study.	Cryptorchidism	Turquey	No	Association between cryptorchidism, testicular atrophy and fertility	/	/	
Case-control, Wrong exposition, Discussion	Reproduction rates prior to diagnosis of testicular cancer: Does the testicular dysgenesis syndrome exist? Cvancarova, 2011.	Case-control Study.	Cryptorchidism	Norway	No	Association between TDS (cryptorchidism) and testicular cancer (no scrotal temperature linked)	/	/	

Cohort Study. Wrong exposition: Discussion.	Risk of testicular cancer in cohort of boys with cryptorchidism. Swerdlow, 1997.	Cohort study. Setting: Hospital for Sick Children, Great Ormond Street, London. Subjects: 1075 boys with cryptorchidism treated by orchidopexy or hormones at the hospital during 1951-64.	Cryptorchidism	United Kingdom	No	Association between cryptorchidism and testicular cancer (no scrotal temperature linked)	Main outcome measures: Relative risk of testicular cancer in the cohort compared with men in the general population.Objective: To determine the risk of testicular cancer in relation to undescended testis and its treatment based on recorded details of the maldescent, treatment, and biopsy from case notes.	/	Results: 12 testicular cancers occurred in 11 of the patients during follow up to mid-1990 (relative risk of cancer in males with cryptorchidism=7.5 (95% confidence interval 3.9 to 12.8)). The relative risk fell significantly beyond 15 years after orchidopexy but did not decrease with younger age at orchidopexy. Risk was significantly raised in testes that had had biopsy samples removed during orchidopexy (relative risk=66.7 (23.9 to 143.3) compared with a testis in a man in the general population) and was significantly greater in these testes than in undescended testes that had not had biopsy samples taken at orchidopexy (6.7 (2.7 to 13.5)). No reasons for biopsy or distinguishing clinical aspects of the testes that had had biopsy samples taken and later developed malignancies were evident in the case notes. No histological abnormalities were evident at initial biopsy except in one testis that had features of dysgenesis.Conclusions: Biopsy seems to be a stronger risk factor for testicular cancer than any factor previously identified. The trauma of open biopsy may contribute substantially to risk of malignancy or the testes may have been selected for biopsy on the basis of clinical factors predictive of malignancy but not mentioned in the case notes. The reasons for increased risk of testicular cancer in cryptorchidism are unclear Risk of testicular cancer was determined in follow up of 1075 boys with cryptorchidism treated during 1951-64 The relative risk of testicular cancer in the cohort compared with men in the general population was 7.5 and did not decrease with younger age at orchidopexy Risk was much greater in undescended testes from which a biopsy sample had been taken during orchidopexy than in those with no biopsy Biopsy was a stronger risk factor for testicular cancer than any factor previously identified
Review, Discussion	Cryptorchidism and Testicular Cancer: Separating Fact From Fiction. Hadley M. Wood and Jack S. Elder, 2009.	Systematic review.	Cryptorchidism	Mondial	No	Association between age of orchydopexy and testicular cancer (no scrotal temperature linked)	/	/	The RR of testicular cancer in a cryptorchidism case is 2.75 to 8. A RR of between 2 and 3 has been noted in patients who undergo orchiopexy by ages 10 to 12 years. Patients who undergo orchiopexy after age 12 years or no orchiopexy are 2 to 6 times as likely to have testicular cancer as those who undergo prepubertal orchiopexy. A contralateral, normally descended testis in a patient with cryptorchidism carries no increased risk of testis cancer. Persistently cryptorchid (inguinal and abdominal) testes are at higher risk for seminoma (74%), while corrected cryptorchid or scrotal testicles that undergo malignant transformation are most likely to become nonseminomatous (63%, p 0.0001), presumably because of a decreased risk of seminoma. Conclusions: Orchiectomy may be considered in healthy patients with cryptorchidism who are between ages 12 and 50 years. Observation should be recommended in postpubertal males at significant anesthetic risk and all males older than 50 years. While 5% to 15% of scrotal testicular remnants contain germinal tissue, only 1 case of carcinoma in situ has been reported, suggesting that the risk of malignancy in these remnants is extremely low.
Cohort Study. Wrong exposition: Discussion.	Early life risk factors for testicular cancer: a casecohort study based on the Copenhagen School Health Records Register Johanne Spanggaard Piltoft. 2017.	Cohort Study.	Cryptorchidism	Danemark	No	Association between cryptorchidism, birth's position, and testicular cancer (no scrotal temperature linked)	/	/	The study found a higher and significant estimate of RR of testicular cancer among men with persistent cryptorchidism (OR ¼ 4.3, 95% CI 1.9–9.7) than with cryptorchidism with spontaneous descent (OR ¼ 1.4, 95% CI 0.6–2.9) relative to a reference group with no cryptorchidism. The present study verify the well established association between cryptorchidism and testicular cancer in a large population-based dataset spanning several decades of birth cohorts. Furthermore, the study contributes with the finding that this association persists after taking birth weight and birth order into account, and thus these factors do not seem to be important confounders. The study finds supporting evidence of an inverse association between birth weight and testicular cancer, and no clear association between birth order and testicular cancer
Cohort Study. Wrong exposition: Discussion.	Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome Daniel S Engeler, 2000.	Cohort Study. Testicular biopsies (n = 660) from 440 prepubertal patients with cryptorchidism who underwent orchiopexy between January 1, 1970 and December 31, 1979 were evaluated for ITGCNU using placental-like alkaline phosphatase (PLAP) antibody.	Cryptorchidism	Danemark	No	Association between age of orchidopexy and fertility, and association between prior intra tubular neoplasie and testicular cancer. (no scrotal temperature linked)	/	/	The clinical outcome in 15 patients with PLAP-positive germ cells was evaluated in 1997. In addition, the effect of age at surgery on the fertility of patients with bilateral cryptorchidism was assessed by clinical follow-up until 1997 and was correlated with the histologic data at orchiopexy. Results. PLAP-positive germ cells morphologically identical with adult ITGCNU were found in the biopsies of 22 patients (5%). After more than two decades, none of the 15 patients with successful follow-up developed testicular cancer. The fertility outcome in the patients with bilateral cryptorchidism correlated with the number of spermatogonia at orchiopexy (P = 0.018), but correlated inversely with age at orchiopexy (P = 0.021). Conclusions. PLAP-positive germ cells in prepubertal testicular biopsy specimens are not necessarily precursors of testicular cancer after orchiopexy. In addition, our data support the idea that early orchiopexy may be beneficial in preventing infertility.
Case-control, Wrong exposition, Discussion	Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. Marie Walschaerts, Audrey Muller, 2007.	Case-control Study.	Cryptorchidism	France	No	Association between enverionemental factors and testicular cancer (no scrotal temperature linked)	/	/	Cryptorchidism was associated with an increased risk of TC, as already found by numerous authors (Moller et al., 1996; McGlynn, 2001). Interestingly, they observed a significantly higher risk of TC if there was a family history of cryptorchidism, TC or breast cancer.An odds ratio of 9.58 [CI: 4.01–22.88] was found for TC in relatives, with a significant increase if there was TC in the father (22.23; CI: 2.56–192.59). Nevertheless, and although the genetic hypothesis deserves to be considered, it is difficult to disregard the environmental component in family history of TC.

Case-control, Wrong OC, Discussion	[Testicular cancer and cryptorchidism: myth or reality] A L Castillo Fernández 1, R M Paredes Esteban, V Vargas Cruz, C Ruiz Hierro, C E Lasso Betancor, O D Gómez Beltrán, J I Garrido Pérez. 2012	Case-Control Study. 175 patients diagnosed with testicular cancer, from 1999 to 2010. They analyzed the previous history of cryptorchidism and its characteristics, testicular placing, histology and intervention age.	Cryptorchidism		No	Association between cryptorchidism and testicular cancer (no scrotal temperature linked)	/	/	Evaluate the previous history of cryptorchidism in patients with testicular cancer. 5 out of the 175 patients (2,8%) with testicular neoplasm presented a history of cryptorchidism, The average age was 31 years old, an orchidopexy was only carried out in 2 patients. The histology was different depending on the treatment chosen to battle cryptorchidism and in 2 cases it developed in the adjoining testicle. The average ratio was of 1,9. Results reflect that the association of cryptorchidism with testicular neoplasm is in fact lower than in the past. A good and proper handling of cryptorchidism can prevent it from turning malignant, presenting these patients similar incidences to the rest of the population.
Cohort Study. Wrong OC: Discussion.	Testicular Cancer Risk in Boys with Maldescended Testis: A Cohort Study. Aleksander Giwercman, 1987	Cohort study. The study population consisted of boys with maldescended testis, also known as cryptorchidism. The patients included in the exposed cohort were those who had been hospitalized for this specific condition over a certain period. These boys were followed from the time of their hospital admission for maldescended testis. Comparator was the general male population of Danemark.	Cryptorchidism	Danemark	No	Association between cryptorchidism and testicular cancer (no scrotal temperature linked)	RR = 4,7 (IC: 1,7-10,2)	/	risk of testicular cancer in boys with maldescended testis, the researchers found that male subjects with a history of testicular maldescent had a significantly increased risk of testicular cancer compared to the general population. The relative risk was 4.7 (95% confidence interval 1.7 to 10.2), indicating a nearly fivefold higher risk for testicular cancer in these individuals. The study also noted a higher relative risk in patients with bilateral maldescent compared to unilateral maldescent, although this difference was not statistically significant due to the limited sample size. The types of testicular cancer observed in the study population were predominantly seminomas and embryonal carcinomas. The median age at diagnosis was 32.8 years, with no cases of testicular cancer observed before the age of 20. The study did not support the recommendation of removing all unilaterally maldescended testes, citing advancements in testicular neoplasm treatment and the ability to diagnose testis cancer at a pre-invasive stage. Overall, the findings of this investigation align with previous case-control studies, indicating a 4 to 5 times higher risk of testicular malignancy in boys with maldescended testis. The study contributes valuable insights into the association between cryptorchidism and testicular cancer risk, highlighting the importance of continued monitoring and research in this area.
Case-Control, RR significant	2) Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia, Linda M. Pottern, 1985.	Case-control study. Included 271 cases of testicular cancer and 259 controls,men aged 18-42 years, all referred to three collaborating medical centers in the Washington, DC, area, to assess the relative risk associated with a history of undescended testis and hernia repair.	Cryptorchidism	USA	Yes	Association between increased temperatur e related to cryptorchidism and testicular cancer	RR=3,7 (IC = 1,6-8,6)	Yes	This study aimed to investigate the relationship between cryptorchidism (undescended testis) and the risk of testicular cancer among young men. The research was conducted through a case-control study involving men aged 18-42 who were referred to three medical centers in the Washington, DC area. Testicular cancer cases diagnosed between 1976 and 1981 were compared with controls diagnosed with cancers other than genital tract cancer during the same period. The study found a significant association between a history of cryptorchidism and testicular cancer, with a threefold increased risk for men who had undergone orchiopexy (surgical correction of undescended testis). The risk of testicular cancer was observed to increase with age at correction of cryptorchidism, indicating a direct relationship between the age of corrective surgery and cancer risk. The analysis also revealed a lack of elevation in risk for the contralateral testis, suggesting that internal factors affecting the retained testis in the body may be responsible for the increased cancer risk, rather than a congenital predisposition. Furthermore, the study highlighted the potential role of increased testicular temperature or other exposures related to the presence of an undescended testis in the body in contributing to the elevated risk of testicular cancer. These findings support the recommendation for early surgical correction of cryptorchidism to reduce the risk of testicular cancer. The study's results underscore the importance of understanding the mechanisms linking cryptorchidism, testicular cancer, and the impact of corrective surgery on cancer risk.
Case-Control, Wrong exposition	Is the incidence of testis cancer related to trauma or temperature? A. J. Swerdlow, 1988	Case-control study : 259 patients with testis cancer. Comparators were Two sets of control patients without testis cancer randomly selected ine the same area.	External Heat	UK	Yes	Association between temperature and testicular cancer.	Brief (jockey type) underpants: RR = 1.17 (95% confidence interval: 0.72-1.91) Occupational high temperature exposure: RR = 1.03 (95% confidence interval: 0.7-1.51) Sleeping in underpants: RR = 0.96 (95% confidence interval: 0.59-1.55) Occupational low temperature exposure: RR = 1.14 (95% confidence interval: 0.62-2.06)	NO SIGNIFICANT	In the study, the researchers reported the relative risks (RR) for the link between exposure to abnormal temperatures and testicular cancer. Here are the results for some exposures to abnormal temperatures: These results indicate that none of these exposures to abnormal temperatures were significantly associated with the risk of testicular cancer . The key findings of the study conducted by A. J. Swerdlow, Sharon R. A. Hultly, and P. G. Smith regarding the incidence of testis cancer in relation to trauma or temperature are as follows: The study found no significant association between testis cancer and exposure to trauma or temperature. Patients with testis cancer did not show a higher frequency of prior traumatic or temperature exposures compared to control patients without testis cancer. The researchers made efforts to prevent bias in the study by not informing subjects about the specific disease being investigated and avoiding questions that could lead to biased responses. The study concluded that everyday temperature and trauma exposures are not major risk factors for testis cancer. Further investigation is suggested to explore the potential roles of extreme trauma and conditions like cryptorchidism in the development of testis cancer. These findings indicate that commonly encountered exposures to trauma and temperature are unlikely to be significant factors in the etiology of testis cancer. The study concluded that the results suggest that common exposures to abnormal temperatures and testicular trauma are not major etiological factors for testicular cancer. The measures taken to avoid reporting bias and ensure comparability of cases and controls strengthened the validity of the findings. The associations between sports activities and testicular cancer risk were inconsistent, with no significant relationships found. Lastly, the study emphasized the importance of rigorous methodology in assessing risk factors for testicular cancer.

Type étude	Title. Main Author. Year of Publication.	Study Type. Population. Comparator(s).	Type chaleur	Année	Pays	Lien O/N	Obj ppal	Obj p value	CCL O/N	Remarques
Etude observationnelle transversale, Wrong OC : discussion	Familial testicular germ cell tumor: no associated, syndromic pattern identified, Christine M Mueller, 2014.	/		01/02/2014 ; Christine M Mueller 1 , Larissa A Korde 2 , Mary L McMaster 3 , June A Peters1 , Gennady Bratslavsky 4 , Rissah J Watkins 5 , Alex Ling 6 , Christian P Kratz 1 , Eric A Wulfsberg 7 , Philip S Rosenberg 8 and Mark H Greene 1	USA	wrong OC	Lien anomalies syndromiques (hernie inguinale et anomalies Urogénitales)/ Cancer Testiculaire Familial	Prévalence hernie inguinale congénitale chez les patients atteints de tumeurs germinales testiculaires familiales, et leurs parents, comparativment à la population générale	yes	
3) Case-control, RR SIGNIFICANT	germ cell tumours by histological tumo	Case-control study. Population: Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas Comparator: Each case was matched with a control selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	hernie Inguinale	21/06/1905	UK	yes	Association Inguinal hernia (risk factors) and testicular cancer	**Odds ratio (OR) for inguinal hernia:** **For pure seminoma tumors:** OR = 1.60 (95% [CI]: 0.88-2.93) **for other histological types of tumors:** OR = 2.39 (95% CI: 1.28-4.46). **Inguinal hernias diagnosed before the age of 15 :** **for pure seminoma :** OR = 3.12 (95% CI: 1.42-6.88) **for other histologies :** OR = 2.49 (95% CI: 1.06-5.88) **Inguinal hernias diagnosed After the age of 15 :** **for pure seminoma :** OR = 0,56 (95% CI: 0,2-1,6) **for other histologies :**	yes	The article "Risk factors for testicular germ cell tumours by histological tumour type" presents findings from the United Kingdom Testicular Cancer Case-control Study, one of the largest studies on the aetiology of testicular germ cell tumours. The study explores associations with testicular tumour risk, including factors like undescended testis, age at puberty, and exercise habits. The analysis by histological tumour type reveals significant differences in risk factors, providing insights into the aetiology of different tumour types. The study methodology involved interviews, medical history reviews, and pathology report analyses to classify tumours as 'pure seminoma' or 'other histological type'. The study used unconditional logistic regression to estimate odds ratios and identify risks that differed significantly by tumour type. The results highlight the importance of considering histological differences in understanding testicular cancer risk factors. These results suggest a potential association between inguinal hernia and an increased risk of testicular germ cell tumors, particularly for certain histological types.The study investigated the association between risk factors and testicular germ cell tumors by histological tumor type. It found that the risk associated with inguinal hernias diagnosed before age 15 differed between pure seminomas and other histological types. For inguinal hernias diagnosed before age 15, the risk was increased for non-seminomatous tumors but reduced for pure seminomas. The risks associated with inguinal hernias were similar overall for both histological groups, but analysis by age at hernia diagnosis revealed different risk patterns.Previous studies have shown inconsistent results regarding the association between inguinal hernias and testicular cancer risk, with no clear and consistent pattern emerging. The findings of this study suggest that the relationship between inguinal hernias and testicular cancer risk may vary depending on the histological tumor type. Further research is needed to better understand the underlying mechanisms and potential differences in risk factors for different types of testicular germ cell tumors.
2) Case-control, RR SIGNIFICANT	2) Testicular Cancer Risk Among Young Men: Role of Cryptorchidism and Inguinal Hernia, Linda M. Pottern, 1985.	Case-control study. Included 271 cases of testicular cancer and 259 controls,men aged 18-42 years, all referred to three collaborating medical centers in the Washington, DC, area. Comparators were men with testicular cancer (cases) to men without testicular cancer (controls) to assess the relative risk associated with a history of undescended testis and hernia repair.	hernie Inguinale	Fev 1985; Linda M. Pottern, M.P.H.,2,3 Linda Morris Brown, M.P.H., 2 Robert N. Hoover, M.D., 2 Nasser Javadpour, M.D.,4 Kevin J. O'Connell, M.D.,5 Ray E. Stutzman, M.D.,6 and William A. Blattner, M.D. 2,7	USA	yes	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	Inguinal hernia before 7 years old: RR = 1,5 (IC 95% : 0,8-2,7) Inguinal Hernia after 7 years old: RR = 6,1 (IC 95%: 1-43,9)	yes	The study, conducted in the Washington, DC area, aimed to investigate the relationship between cryptorchidism, inguinal hernia, and the risk of testicular cancer in young men aged 18-42. A large case-control study was carried out involving 271 cases of testicular cancer and 259 controls. Subjects were selected from three collaborating medical centers, and detailed information was obtained through interviews and medical records. The study found a higher risk of testicular cancer in men with a history of undescended testes, especially if the condition was not corrected. Additionally, men who underwent hernia surgery after age 7 had an elevated risk of testicular cancer on the same side as the hernia. The study supported the importance of early surgical correction of cryptorchidism and inguinal hernia to reduce the risk of testicular cancer. The study found that there was no substantial excess risk of testicular cancer for men without cryptorchidism who had undergone hernia repair. However, for those who had hernia repair at older ages (28 years and above), there was an elevated risk of testicular cancer on the same side as the hernia. This elevated risk was particularly notable for bilateral hernia repairs. The study suggests that this increased risk may be due to delayed correction of undescended testes or other factors related to late hernia repair. Further research is recommended to explore the potential implications of this finding for preventive measures and understanding the underlying causes of testicular cancer. In the discussion, the study highlighted that while previous research had shown a relationship between inguinal hernia and testicular cancer risk, the association was not well-defined. The study's findings indicated that men without cryptorchidism who had undergone hernia repair did not experience a significant excess risk of testicular cancer. However, there was an elevated risk associated with hernia repair at older ages (28 years and above), particularly for cancers that developed on the same side as the hernia. The study proposed several explanations for this finding, including the possibility of chance, the impact of late correction of undescended testes among individuals with both hernia and cryptorchidism, or the potential risk elevation due to delayed correction. The study recommended further investigation into this topic for its preventive implications and insights into the causes of testicular cancer.

4)Case-control, RR SIGNIFICANT	4) Congenital malformations and testicular germ cell tumors, Britton Trabert, 2013.	Population-based case-control study conducted in Sweden. The population included individuals diagnosed with testicular germ cell tumors (cases) and matched controls without the tumors. The comparator used in the study was individuals without testicular germ cell tumors, serving as the control group for comparison.	hernie Inguinale	12/04/2013, Britton Trabert1*, Daniela Zugna2*, Lorenzo Richiardi2, Katherine A. McGlynn1 and Olof Akre2 Nasser Javadpour, M.D.,4 Kevin J. O'Connell, M.D.,5 Ray E. Stutzman, M.D.,6 and William A. Blattner, M.D.	Sweden	yes	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	OR =1,37 (IC 95%: 1,11-1,68)	yes	The study was conducted in Sweden using population-based registry data. It aimed to investigate the association between congenital malformations and testicular germ cell tumors (TGCT). A total of 7,552 TGCT cases diagnosed between 1964 and 2008 were included, along with 32,955 controls matched for year and county of birth. Hospitalization records were used to identify congenital malformations, and statistical analysis was performed using conditional logistic regression. The study found that hypospadias, inguinal hernia, and other genital malformations were associated with an increased risk of TGCT, supporting the hypothesis that prenatal exposures affecting proper genital development may be related to the development of these tumors. The study found that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, are associated with an increased risk of testicular germ cell tumors (TGCT) . Specifically focusing on inguinal hernia, the analysis revealed that there is an elevated risk of TGCT associated with inguinal hernia, even after accounting for the association between cryptorchidism and TGCT . This suggests that inguinal hernia may independently contribute to the risk of developing testicular cancer. In the discussion, the study highlighted that developmental urogenital abnormalities, including cryptorchidism, hypospadias, and inguinal hernia, were linked to an increased risk of testicular germ cell tumors (TGCT), supporting the notion that prenatal exposures affecting proper genital development may play a role in TGCT etiology . The findings also suggested that the associations between these abnormalities and TGCT risk may represent distinct etiologic pathways, with inguinal hernia showing consistent increased risks across various studies . Additionally, the study discussed the potential implications of early diagnosis of malformations, such as hypospadias, on the severity of defects and their relation to TGCT risk.
5) Case-control, RR SIGNIFICANT	5) Cryptorchidism, hernia, and cancer of the testis. Alan S. Morrison, 1976.	Case-control Study A total of 596 patients with testicular cancer and 602 unaffected controls, who had served in the U.S. military between 1950 and 1970, were studied based on the medical histories and military records of the participants.	hernie Inguinale	1976	USA	yes	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	RR: 2,9 (IC à 95%: 1,3-7,0)	yes	The study focused on young adults serving in the Army, and the data collection process ensured that information on undescended testis and other exposures was obtained consistently for cases and controls. The risk ratio estimate for testicular cancer associated with undescended testis was 8.8, with previous studies suggesting a risk ratio closer to 10.The study found that men with a history of undescended testis had a significantly higher risk of testicular cancer, with a risk ratio estimate of 8.8. Additionally, individuals who had undergone hernia operation before age 15 were 2.9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed. Furthermore, undescended testis was closely associated with the side of the testicular tumor, with tumors often occurring in the testis that had been undescended. Histologically, tumors in patients with undescended testis were more likely to be seminomas compared to other types of tumors. The data suggested a moderate elevation of risk among subjects with repaired hernias, indicating a potential link between inguinal hernia and testicular cancer risk. Further research is warranted to explore the relationship between inguinal hernia and the risk of testicular cancer in more detail. The discussion highlighted three peaks in testicular cancer morbidity and mortality: at 2 years of age, early adulthood, and old age. The study also discussed the potential causal relationship between undescended testis and testicular cancer, emphasizing the need for further research, especially regarding the impact of surgical correction of undescended testis on testicular cancer rates. The study found a significant association between undescended testis and an increased risk of testicular cancer, with a risk ratio estimate of 8.8. Individuals who had undergone hernia operation before age 15 were 2.9 times more likely to develop testicular cancer. The side of the hernia was not related to the side of the tumor that followed, and hernia was not associated with tumors of a specific histologic type. The discussion emphasized the peaks in testicular cancer morbidity and mortality at different ages and highlighted the need for further research to explore the causal relationship between undescended testis, hernia, and testicular cancer

Case-control Study, OC : RR NO significant	6) Genital anomalies and risk for testicular cancer in Danish men. A Prener, 1996.	183 cases of testicular cancer registered in the Danish Cancer Registry. For each case, 2 age- and sex-matched controls were selected, resulting in a total of 366 controls. In a cohort of Danish boys characterized by being born between 1941 and 1957, having attended schools in a defined area of Denmark, and having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985	hernie Inguinale	1996, .A Prener 1, G Engholm, O M Jensen	Danemark	yes	Association between urogenital abnormalities and testicular cancer	Inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7)	no significant	In a cohort of Danish boys characterized by (1) being born between 1941 and 1957, (2) having attended schools in a defined area of Denmark, and (3) having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985. We selected 366 age- and sex-matched controls from the same cohort. Using information recorded by school physicians, we performed logistic regression analyses to estimate the relative risks (RR) associated with various genital anomalies. We found the risk for testicular cancer to be raised for men with a history of cryptorchidism [RR = 5.2; 95% confidence interval (CI) = 2.1-13.0], inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7), hypospadias (RR = 4.2; 95% CI = 0.4-42.7), and hydrocele (RR = 2.4; 95% CI = 0.6-9.0). We observed no decrease in the risk associated with cryptorchidism after correction of the maldescent in early childhood. The RR of testicular cancer in the contralateral, normally descended testis in unilateral cryptorchid men was increased to 3.6. The results add to the growing evidence for a common causal factor for both testicular cancer and cryptorchidism and support the findings from other studies of associations between other genital anomalies involving the closure of the processus vaginalis and the risk of testicular cancer.
Case-control Study, OC : RR NO significant	7) Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. A.J. Swerdlow, 1982	Case-control study based on 87 deaths from testicular cancer in children in Great Britain from 1953 to 1973. The cases were children who died from testicular cancer, while the controls were children who died from other causes.	hernie Inguinale	1982	UK	yes	Association between urogenital abnormalities and testicular cancer	RR = 2.05, p-value >0.05	no significant	For inguinal hernia, the relative risk (RR) was 2.05 with a p-value >0.05, indicating no significant risk associated with inguinal hernia. For hydrocele, the RR was 2.99 with a p-value of 0.15, also suggesting no significant risk associated with hydrocele. It is important to note that these results did not show a significant association between these specific genitourinary anomalies and the risk of testicular cancer in children.
Case-control, RR SIGNIFICANT	8) Sports activities and risk of testicular cancer. A. J. Coldman, 1982	Case-control study, Men with testicular seminoma (cases) and men without testicular cancer (controls). The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk.	hernie Inguinale	1982	Canada	yes	association between inguinal hernia and risk of testicular cancer	(RR) = 2,86 (IC 95 % : 1,24 - 6,74)	significant	The study examined characteristics of childhood and adolescence in a case-control study of patients treated for testicular seminoma at a regional treatment center between 1970-77. A total of 128 seminoma patients were included, matched with controls diagnosed with skin cancer or Hodgkin's disease. Data collection involved reviewing medical records and obtaining detailed occupational histories. No significant differences were found in sibship size, parental age at subject's birth, infectious diseases, or hormone imbalance conditions. Socio-economic status and urban-rural residence also did not show a relationship with case-control status. The study utilized questionnaires and statistical analyses to investigate potential risk factors associated with testicular seminoma.The study compared the history of inguinal hernia between men with testicular seminoma and those without testicular cancer to assess the association between inguinal hernia and testicular cancer risk.The study found a significant association between a history of inguinal hernia and testicular cancer. Patients with testicular seminoma who reported a history of inguinal hernia had a higher risk of developing testicular cancer compared to controls. Even after controlling for cryptorchidism, the overall risk remained elevated. The effect of inguinal hernia varied with age at diagnosis, with those diagnosed before the age of 15 having a much higher risk than those diagnosed after that age. The findings suggest that a history of inguinal hernia, especially occurring at a young age, may be an important risk factor for the subsequent development of testicular cancer. This highlights the significance of considering postnatal risk factors, such as inguinal hernia, in assessing the risk of testicular cancer. Further research is warranted to explore the underlying mechanisms linking inguinal hernia to testicular cancer and to better understand the implications of this association for cancer prevention and early detection strategies.

Case-control, RR SIGNIFICANT	9) The epidemiology of testicular cancer in upstate New York . Brenda P. Haughey, 1989.	observational case-control study . The population studied included individuals from upstate New York between January 1977 and June 1980 . The study compared individuals diagnosed with testicular cancer (cases) to individuals without testicular cancer (controls) to identify potential risk factors associated with the disease	hernie Inguinale	1989	USA	yes	Association Inguinal hernia (risk factors) and testicular cancer	OR = 2.17, (IC 95% : 1.3 - 4.4)		The study on testicular cancer in upstate New York found significant associations between certain factors and testicular cancer risk. Factors such as exposure to high temperatures at work, bathing preference, history of diseases associated with high fever, occupational exposures to fertilizers, phenols, and fumes or smoke, as well as testicular trauma from activities like riding a bicycle or motorcycle, were linked to increased odds of testicular cancer. Specifically, individuals with a history of hernia showed an odds ratio of 2.17 for testicular cancer, indicating a significant association . These findings suggest that both environmental and personal factors may play a role in the development of testicular cancer. The study highlights the importance of considering various exposures and medical histories when assessing the risk of this type of cancer. Further research and awareness of these risk factors could aid in early detection and prevention strategies for testicular cancer.
Case-control Study, OC : RR NO significant	10) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987.	Case-control study Population studied: 259 cases of testicular cancer, 238 men with other diagnoses attending the same radiotherapy centers as the cases, and 251 hospitalized patients not attending radiotherapy services. Comparators: Two control groups - men with other diagnoses attending the same radiotherapy centers as the cases, and hospitalized patients not attending radiotherapy services.	hernie Inguinale	1987	UK	yes	Association between inguinal hernia, mumps orchitis, infection and testicular cancer.	Inguinal Hernia : RR = 1.6 (p = 0.14)	no significant	The case-control study on the etiology of testicular cancer conducted by Swerdlow et al. (1987) involved 259 cases of testicular cancer, 238 men with other diagnoses, and 251 hospitalized patients. The study found an increased risk of testicular cancer associated with a history of mumps orchitis (RR = 12.7, p = 0.006) and atopy (RR = 1.8, p = 0.03). Inguinal hernia showed a relative risk of 1.6, although it was not statistically significant. The study did not provide specific relative risk values for other urogenital malformations. The discussion highlighted the challenges in accurately determining past testicular position in cryptorchidism cases and the potential biases in case-control studies related to this issue. Further research, particularly cohort studies, was suggested to provide more reliable data on malignancy risks in cryptorchidism. The association between inguinal hernia and undescended testis was noted, but the extent to which this explains the increased risk of testicular cancer associated with hernia remains unclear. Discussion: The study results underscore the importance of considering factors such as mumps orchitis and atopy in assessing the risk of testicular cancer. The challenges in accurately determining past medical history, especially in cryptorchidism cases, highlight the need for more robust study designs like cohort studies. The discussion also addresses the potential confounding factors related to inguinal hernia and undescended testis, emphasizing the need for further research to elucidate the mechanisms underlying the observed associations.

Case-control, RR SIGNIFICANT	11) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case-control studies in Denmark. Henrik Møller, 1995	Case-control study Cases were Men born in Denmark between 1916 and 1970, with testicular cancer diagnosed between 1986 and 1988, frequency-matched controls by year of birth, from the Danish Central Population Register. Cryptorchidism cases identified from two hospital-based case series. Cryptorchidism controls identified from the general population.	hernie Inguinale	1995	Denmark	yes	Association between inguinal hernia, testicular atrophy and testicular cancer.	Inguinal hernia: RR = 1,4, (IC 95% :1,0 - 2,1)	significant	11) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case-control studies in Denmark. Henrik Møller, 1995. The study conducted in Denmark aimed to investigate the association between cryptorchidism and testicular cancer. Data collection involved contacting men by mail and conducting telephone interviews. Information on cryptorchidism, inguinal hernia, testicular atrophy, and other congenital malformations was gathered. The data were analyzed using contingency tables and logistic regression analysis, with controls frequency-matched to cases by year of birth. The study found associations between testicular cancer and cryptorchidism, as well as testicular atrophy. The relative risk of testicular cancer was higher in men with a history of testicular atrophy. The study also highlighted the importance of early treatment for cryptorchidism and its potential impact on the risk of testicular cancer.The study found that inguinal hernia was weakly associated with testicular cancer overall, with an odds ratio (OR) of 1.4 and a 95% (CI) of 1.0-2.1. However, when the analysis was restricted to reported inguinal hernia in the absence of cryptorchidism or testicular atrophy, the association disappeared . This suggests that the association between inguinal hernia and testicular cancer may be influenced by the presence of other conditions such as cryptorchidism or testicular atrophy. In the discussion, it was noted that the association with inguinal hernia was much stronger in one of the series compared to the other, indicating potential differences in the study populations . The study also highlighted that the association between inguinal hernia and testicular cancer was not significant once the analysis was adjusted for other conditions, suggesting that the presence of cryptorchidism or testicular atrophy may confound the relationship between inguinal hernia and testicular cancer. Overall, the results and discussion suggest that while there may be a weak association between inguinal hernia and testicular cancer, this association is influenced by the presence of other conditions such as cryptorchidism or testicular atrophy.
Case-control Study, OC : RR NO significant	12) Testicular cancer in young men: the search for causes of the epidemic increase in the United States. Linda Morris Brown, 1987.	Case-control study. The study population included 271 men with testicular cancer and 259 controls in the Washington, DC area. Cases were men aged 18-42 who were newly diagnosed with testicular cancer between January 1976 and June 1981 and were referred to three collaborating medical centers in the Washington, DC area. Controls were selected from the same geographical area. as the cases, allowing for the comparison of various factors between the two groups to assess potential associations with testicular cancer risk.	hernie Inguinale	1987	USA	yes	Association between inguinal hernia, mumps orchitis, infection and testicular cancer.	Inguinal Hernia : RR = 1,2 (IC 95%: 0,6-2,7)	no significant	The study investigated various factors potentially related to the risk of testicular cancer in young men and aimed to evaluate if any of these factors could explain the significant increases in testicular cancer incidence over time. Factors such as sociodemographic characteristics, childhood residence, religion, and external factors affecting testicular temperature were examined. The study found a slight excess risk for individuals spending their childhood in urban areas compared to rural areas. While there was an apparent excess of Mormons with testicular cancer, it was not statistically significant. External factors like the type of underwear worn or bathing habits did not show significant differences between cases and controls. Additionally, individuals with undescended testis were found to be at an increased risk for developing testicular cancer. However, the association between mumps orchitis and testicular cancer was not statistically significant. Regarding a history of hernia and testicular cancer, the study did not find a substantial risk associated with a history of groin hernia operation. This lack of significant association suggests that a history of hernia may not be a strong risk factor for testicular cancer in the studied population.
Case-control Study, Wrong OC, discussion	13) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. Tollerud, 1985.	Case-control study. Newly diagnosed cases of testicular cancer referred to three participating hospitals from January 1976, through June 1981, and controls with similar characteristics of age, sex, and race selected from individuals with other forms of cancer hospitalized at the same institutions	hernie Inguinale	1985; DAVID J . TOLLERUD, MD,' WILLIAM A. BLATTNER. MD,' MARY C. FRASER, RN. MA,' LINDA MORRIS BROWN, MPH,' LINDA POTTERN, MPH,' ELLEN SHAPIRO, MD,' AARON KIRKEMO, MD,' THOMAS H. SHAWKER, MD,' NASSER	USA	wrong OC	Association between family history of urogenital anomalies in close relatives of patients and testicular cancer.	SIR:3,9 (IC 95%: 1,7-9)	yes	Focuses on the family history of urogenital anomalies in close relatives of patients with testicular cancer, such as inguinal hernia, cryptorchidism, varicocele, hydrocele, etc. It explores how these family histories may be related to the risk of developing testicular cancer. The study was a case-control study that examined the occurrence of testicular cancer and urogenital anomalies in family members. Six familial clusters with testicular cancer in first-degree relatives were identified. Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis . 6 out of 269 testicular cancer cases (2.2%) had a first-degree relative with testicular cancer, compared to 1 out of 259 controls (0.4%) . Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population . Cryptorchidism was reported in 17% of familial cases, 2.7% of controls, and 5.3% of cases with no family history of testicular cancer . The presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia

Retrospective Cohort : OC, RR NO Significant	14) CONGENITAL ANOMALIES IN CHILDREN WITH TESTICULAR GERM CELL TUMOR, Shiego Sakashita, 1980.	Retrospective cohort. The study compared cases of testicular germ cell tumors in children who had undergone orchiectomy at the hospital . Children with testicular germ cell tumors who had congenital anomalies to those without such anomalies to assess the association between tumor development and the presence of congenital abnormalities.	hernie Inguinale	1980; SHIGEO SAKASHITA, TOMOHIKO KOYANAGI, * ICHIRO TSUJI, KATSUHISA ARIKADO AND TADASHI MATSUNO	Japan	yes	Association between Inguinal hernia, Cryptorchidism and Testicular Cancer	Unknown	RR No significant	The study retrospectively analyzed 25 patients with testicular germ cell tumors, including 20 cases of yolk sac tumors and 5 cases of teratomas. Among these patients, congenital anomalies were observed in 3 individuals with yolk sac tumors and 1 individual with a mature teratoma. The identified abnormalities included a retrocaval ureter, diverticulum of the bladder, Down's syndrome, and an ipsilateral inguinal hernia. In the study, it was observed that among the 25 children with testicular germ cell tumors, 4 patients (16%) had associated congenital malformations. Among these anomalies, inguinal hernia was the most common, with an estimated incidence of 10% among children with testicular tumors. The results suggest that there may be a link between tumor development and the presence of congenital anomalies in children with testicular tumors. Therefore, it is recommended to carefully examine young patients with testicular tumors for potential congenital abnormalities In the discussion, the study highlighted the differences in etiology, pathology, and clinical features of pediatric testicular germ cell tumors compared to adult cases. The predominant tumors in children were teratomas and yolk sac tumors, with a better prognosis in children than in adults. The study suggested that the oncogenesis of testicular tumors in infants may begin in utero. The findings underscored the need for vigilance in identifying congenital anomalies in children with testicular tumors.
Retrospective Cohort : OC, RR NO Significant	15) Familial Testicular Cancer in a Single-centre Population. D.J.A. Sonneveld, 1999.	Retrospective cohort study in a single-center population. The study population consisted of patients with testicular cancer and their affected first-degree, second-degree, or third-degree relatives. The study compared the occurrence of familial testicular cancer cases with the prevalence of testicular cancer in the general population and assessed the association of urogenital developmental anomalies in familial cases compared to non-familial cases. Comparator was the total cohort.	hernie Inguinale	1999; D.J.A. Sonneveld, 1 D.Th. Sleijfer, 2 H. SchraVordt Koops, 1 R.H. Sijmons, 3 W.T.A. van der Graaf, 2 W.J. Sluiter 2 and H.J. Hoekstra	Netherlands	yes	Association between urogenital abnormalities and testicular cancer	Prevalence of a history of inguinal hernia : 3 patients (8.3%) among familial testicular cancer. Do not mention a specific calculation of relative risk or other measures of association to assess the link between inguinal hernia and testicular cancer.	RR No significant	The study retrospectively analyzed familial testicular cancer cases in a single-center population of 693 patients treated between 1977 and 1997. It aimed to assess the proportion of familial testicular cancer cases and estimate the relative risk for first-degree relatives of patients. Additionally, the study evaluated the occurrence of bilateral testicular neoplasms and urogenital developmental anomalies in families with a predisposition to testicular cancer. The results showed that 3.5% of patients had a first-degree relative with testicular cancer, with a total of 24 familial cases belonging to 17 families. The study highlighted the presence of inguinal hernias in 8% of familial cases with affected first-degree relatives. Results regarding inguinal hernia from the study are as follows: 3 patients (8.3%) with familial testicular cancer had a history of inguinal hernia. In familial cases with affected first-degree relatives, inguinal hernias were present in 8% of cases. The study found that the proportion of urogenital developmental anomalies, such as undescended testis (UDT) and inguinal hernias, was slightly higher in familial testicular cancer cases compared to historical general testicular cancer cases. However, these figures were not significantly different from non-familial cases reported in the literature. The presence of UDT in 17% of testicular cancer cases with affected second- or third-degree relatives suggests an association between UDT and familial occurrence of testicular cancer. It is noted that there may be bias in ascertainment due to over-reporting of relatives with these anomalies. Previous studies have also highlighted a high prevalence of urogenital developmental anomalies in familial testicular cancer cases and their first-degree relatives.

Retrospective Cohort : OC, RR NO Significant	16) Occurrence of testicular cancer in patients operated on for cryptorchidism and inguinal hernia. Pinczowski, 1991	Retrospective cohort, 2 population-based cohorts comprising 2,918 men who underwent an operation for a cryptorchid testis and 30,199 who underwent surgery for an inguinal hernia. Complete follow up during the 19-year period was achieved by record linkage to the National Swedish Cancer Registry.	hernie Inguinale	1991	Sweden	yes	association between inguinal hernia and risk of testicular cancer	RR = 1.1, 95% confidence interval 0.4 to 2.2)	RR No significant	Studied the incidence of testicular cancer in 2 population-based cohorts comprising 2,918 men who underwent an operation for a cryptorchid testis and 30,199 who underwent surgery for an inguinal hernia. Complete followup during the 19-year period was achieved by record linkage to the National Swedish Cancer Registry. In the cryptorchidism cohort 4 cases of testicular cancer occurred versus 0.54 expected, yielding a relative risk of 7.4 (95% confidence interval 2.0 to 19.0). Of these patients 3 had undergone a bilateral operation due to intra-abdominal testes. There was no evidence of an association between inguinal hernia and risk of testicular cancer (relative risk = 1.1, 95% confidence interval 0.4 to 2.2). The validity of our data was further supported by relative risk estimates close to unity in a comparison group of appendectomy patients. We conclude that patients with a cryptorchid testis experience a substantially increased relative risk of testicular cancer. However, the low absolute risk, 4 cases during 25,360 person-years of observation, does not appear to justify special surveillance after an operation for an undescended testis.
Retrospective Cohort : OC, RR NO Significant	17) The Relation Between Testicular Tumours, Undescended Testes, and Inguinal Hernias. Th. Wobbes, 1980	Retrospective cohort study examined a group of 230 patients with malignant testicular tumors to investigate the relationship between undescended testes, inguinal hernias, and testicular malignancies.	hernie Inguinale			yes	association between inguinal hernia and risk of testicular cancer	Unknown	no significant	An inguinal hernia was found in 3.4% of the patients with a testicular tumour. This is in agreement with the normal incidence of inguinal hernia [Mustard et al, 19691 Consequently, there seems to be no increased risk for patients with a history of an operaiion for inguinal hernia. But this contradicts Morrison [1967] , who calculated 2.9 times as high a risk of malignant testicular tumour. In the study, it was reported that the risk of malignancy in an undescended testis proved to be about 17 times greater than in the normal population. Regarding inguinal hernia, no increased risk was found for patients with a history of inguinal hernia.

Type étude	N° zotero	Titre	Auteur	Type chaleur	Année	Pays	Lien O/N	Obj ppal	Obj p value	CCL O/N	Remarques
Case-control, OC: RR no significant	https://sci.bban.top/pdf/10.1093/oxfordjournals.aje.a115232.pdf#view=FitH	18) Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Margaret R. KARAGAS, 1989.	Population-based case-control study. Included 323 men with germ cell tumors of the testis diagnosed between 1977 and 1984, as well as 658 selected controls. The comparators in the study were individuals with and without testicular cancer, allowing for the comparison of factors such as intrascrotal temperature elevation and its potential association with the incidence of testicular cancer in noncryptorchid men.	varicocèle	1989, MARGARET R. KARAGAS,'-2 NOEL S. WEISS,1J CLIFTON H. STRADER,3 AND JANET R. DALING	USA	yes	Association between varicocoele and the risk of developing testicular cancer	RR=1,8 (CI 95 %: 0,9 - 3,4)	no significant	The study investigated the potential link between elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. Here is a summary of the results and discussion: No significant association was found between testicular cancer and wearing tight-fitting underwear or heat-resistant clothing at work. A slightly higher proportion of men with testicular cancer reported wearing long underwear for more than three months per year compared to controls. Controls reported more use of hot tubs or saunas than men with testicular cancer. A slightly higher proportion of men with testicular cancer had a history of physician-diagnosed varicocele. The study did not provide strong support for the hypothesis that intermittent intrascrotal temperature elevation contributes to the development of testicular cancer. Previous research has shown that increased intrascrotal temperature can affect spermatogenesis and sperm morphology. Further evaluation is needed to determine if continuous temperature elevation, such as that seen in varicocele, may increase the risk of testicular cancer. These findings suggest that while there may be some associations between intrascrotal temperature and testicular cancer, more research is required to fully understand the potential mechanisms involved.
Retrospective cohort, OC: RR no significant	https://pubmed.ncbi.nlm.nih.gov/36068656/	19) Varicocoele in adolescence and testicular cancer in young adulthood. Guy Verhovsky, 2022.	Nationwide, population-based, historical cohort study. Included 1,521,661 Israeli male adolescents with a mean age of 17.5 years who were screened for varicocoele during the years 1967–2012. Comparators were adolescents with varicocoele stages 2 and 3 to those without varicocoele in terms of the incidence of testicular cancer during young adulthood.	varicocèle	01/02/2022 ; Guy Verhovsky1,2,3,4 Moshe Giladi2,5,6 Dorit Tzur5 Arnon Afek3,6 Lital Keinan-Boker7,8 Estela Derazne6 Dan Kaminsky2 Azik Hoffman9 Tomer Erlich2,10,6,11 Tzahi Neuman	Israel	yes	Association between varicocoele in adolescence and the risk of developing testicular cancer in young adulthood	RR: 0,816 (IC 95% : 0,615 - 1,083)	no significant	Elevated intrascrotal temperature has been suggested as a risk factor for testicular cancer. Varicocele was linked to increased intrascrotal temperature, but whether it is associated with testicular cancer is unclear. We aimed to to explore their potential association. Methods: This nationwide, population-based, historical cohort study includes 1,521,661 Israeli male adolecents (mean age 17.5 ± 0.4 years), who were screened for varicocele as part of their medical assessment prior to compulsory military service during the years 1967-2012. The diagnosis of testicular cancer was ascertained from linkage of records to the the Israeli National Cancer Registry. Logistic regression analysis was applied. Results: In total, 53,210 adolescents were diagnosed with varicocele prior to military service. Of 1,988 (0.13% of the total cohort) men who were diagnosed with testicular cancer, 54 (0.1%) had varicocele prior to military service and 1934 were not exposed to the elevated intrascrotal temperature resulting from varicocele, p=0.314. The age at cancer diagnosis and the distribution of seminomas vs. non-seminomas did not differ significantly between those with and without varicocele in adolescence. Varicocele was also not associated with testicular cancer, in a multivariable analysis controlling for sociodemographic factors. Varicocele in adolecents was not found to be associated with testicular cancer in young adults.

Type étude	N° zotero	Titre	Study Type, Population, Comparator.	Type chaleur	Pays, Année, Auteurs	Pays	Lien O/N	Obj ppal	Obj p value	CCL O/N	Remarques
Epidemiological Cohort OC: RR NO SIGNIFICANT, Data missing, not available	https://explore.openaire.eu/search/publication?pid=10.1016/j.euo.2022.06.009	20) Worldwide Distribution, Risk Factors, and Temporal Trends of Testicular Cancer Incidence and Mortality: A Global Analysis. Huang J, 2011.	Epidemiological Study.	obésité	2011; Huang J; Chan SC; Tin MS; Liu X; Lok VT; Ngai CH; Zhang L; Lucero-Prisno DE 3rd; Xu W; Zheng ZJ; Chiu PK; Ng AC; Enikeev D; Nicol D; Spiess PE; Laguna P; Teoh JY; Wong MCS;	International	Yes	Association between obesity, cholesterol and Testicular Cancer	Not available	Global variation in the testicular cancer burden associated with HDI, GDP, alcohol drinking, inactivity, overweight, obesity, and hypercholesterolaemia. Testicular cancer had an increasing incidence but decreasing mortality.	There was a wide variation in the testicular cancer burden with the highest mortality found in low-income countries, and the regions of Central America and South America, while the highest incidence was observed in high-income countries, especially in Western and Northern Europe. We found a positive association for HDI, GDP, alcohol drinking, inactivity, overweight, obesity, and hypercholesterolaemia with testicular cancer incidence, while a negative correlation was observed between GDP and mortality of testicular cancer. Globally, there was an overall increasing incidence trend of testicular cancer for the past decade, particularly in younger males; the mortality trends of testicular cancer were relatively stable. However, they did not analyse the trend of different stages and subtypes of testicular cancer due to data unavailability. There was a global variation in the testicular cancer burden associated with HDI, GDP, alcohol drinking, inactivity, overweight, obesity, and hypercholesterolaemia. Testicular cancer had an increasing incidence but decreasing mortality. The increasing testicular cancer incidence in the younger population is of concern and calls for early detection and preventive interventions. Globally, testicular cancer incidence had been increasing particularly in the younger population, although its deaths rates had been decreasing. Socioeconomic indices, alcohol drinking, inactivity, overweight, obesity, and high plasma lipid levels are associated with testicular cancer incidence and mortality.
Epidemiological Cohort, OC: RR NO SIGNIFICANT	https://sci-hub.se/10.1007/s11845-010-0643-7	21) Regional variations in testicular cancer rates in Ireland. M. Alsinnawi, 2010.	Epidemiological study. Analyze the incidence of testicular cancer in different counties of Ireland and explore potential risk factors. The population includes individuals diagnosed with testicular cancer in various counties of Ireland between January 1994 and December 2007. The study compares the rates of testicular cancer in Cork County to those in other counties, such as Galway and Meath, to identify significant variations in incidence. The study considers factors such as cryptorchidism, socio-economic status, environmental pollutants, and teenage obesity as they relate to testicular cancer incidence across those different regions.	obésité	01/01/2010	Ireland	Yes	Association between adolescent obesity rates and testicular cancer rates	The distribution of obesity among adolescents in different regions of Ireland did not align with the regional variations in testicular cancer rates.	No significant	Aimed to investigate the incidence of testicular cancer (TCa) in different counties of Ireland between 1994 and 2007. The researchers also explored potential factors such as cryptorchidism, socio-economic status, environmental pollutants, and teenage obesity as risk factors for the development of testicular cancer. Cork County had a significantly higher rate of testicular cancer compared to other counties in Ireland. While high rates of cryptorchidism were observed in Cork, they alone could not explain the elevated incidence of testicular cancer. Areas with higher socio-economic status in Cork showed significantly higher rates of testicular cancer. Organic pollutants linked to testicular cancer were identified in industries located only in Cork. Teenage obesity rates in Cork were not higher than in other regions. Discussion Emphasizing Non-Significant Results: Despite analyzing teenage obesity data as a potential risk factor for testicular cancer, the study did not find a significant association between obesity and testicular cancer incidence. The distribution of obesity among adolescents in different regions of Ireland did not align with the regional variations in testicular cancer rates. This suggests that factors other than obesity may play a more significant role in explaining the observed differences in testicular cancer incidence across counties. Further research is needed to explore the complex interplay of various risk factors contributing to testicular cancer development.

Retrospective Cohort, OC: RR NO SIGNIFICANT	https://sci-hub.yt/10.3109/02841869009089999	22) Body size and cancer of the testis. T.W.Davies, 1990.	Retroscpective population-based cohort study. The study population consisted of 438 cases of testicular cancer and three controls for each case. The data originated from health examinations of men liable for military service in Denmark. The study compared body measurements (height, weight, and body mass index) and aimed to identify any systematic statistically significant differences in body size parameters between the two groups. Comparator was the general population of Danemark.	obésité	1990, T. W. DAVIES, A. PRENER, G. ENGHOL	Danemark	Yes	Association between BMI and Obesity and testicular cancer	IMC>25 <19 years old : RR=0,7 (IC 95%: 0,3-1,3) >19 years old : RR=0,8 (IC 95%: 0,4-1,8)	No significant	22) Body size and cancer of the testis.T.W.Davies, 1990.The study analyzed data from 438 cases of testicular cancer and their controls, investigating the relationship between body size and testicular cancer incidence. The analysis included logistic regression models and categorized body measurements (height, weight, and body mass index) as factors. The study found no systematic statistically significant differences in body measurements between cases and controls. Interestingly, the future victims of testicular cancer were observed to be lighter, smaller, and thinner than unaffected controls, particularly in the younger age group. The difference between cases and controls diminished with increasing age, suggesting that weight gain during adolescence might be a promotional factor for testicular cancer. The study also noted that the social class distribution of cases did not differ significantly from the general population in Denmark. The study did not confirm the initial hypothesis that high fat or calorie intake leading to relative obesity could be a promotional factor for testicular cancer. Instead, the findings indicated a trend where individuals who later developed testicular cancer were lighter, smaller, and thinner than unaffected controls. The authors emphasized the importance of considering body size factors in the context of testicular cancer risk, highlighting the need for further research to understand the complex relationship between body size and cancer development. Additionally, the study noted that the social class distribution of testicular cancer cases in Denmark did not align with findings from other studies associating testicular cancer with higher social class, suggesting potential environmental and lifestyle factors at play in different populations.
Cohort. OC: RR significant	https://sci-hub.se/10.2307/29736546	23) The impact of height and body mass index on the risk of testicular cancer in 600,000 Norwegian men. Tone Bjørge, 2006.	Cohort study. Population consisted of 600,000 Norwegian men, including 557,043 adults and 111,543 adolescents, who were eligible for the study after excluding individuals with a prior diagnosis of testicular cancer. The Comparators was the total cohort.	Obésité	01/01/2006	Norway	Yes	Association between BMI and height, and testicular cancer	**(RR) For adults:** **for seminomas:** BMI: 1.07 (95% CI: 1.00-1.19) **for non-seminomas:** BMI: 1.00 (95% CI: 0.90-1.00) **for all testicular cancer cases:** BMI: 0.66 (95% CI: 0.48-0.90) **(RR)For adolescents:** **for seminomas:** BMI: 1.00 (95% CI: 0.81-1.00) **for non-seminomas:** BMI: 0.88 (95% CI: 0.76-1.03) **for all testicular cancer cases:** BMI: 1.00 (95% CI: 0.76-1.00)	Yes	**The study examined the impact of height and body mass index (BMI) on the risk of testicular cancer in 600,000 Norwegian men. The findings indicated that there was a significant association between height and the risk of testicular cancer, with taller men having a higher risk. Additionally, the study found a U-shaped relationship between BMI and testicular cancer risk, with both underweight and obese men showing an increased risk compared to men with normal BMI. These results suggest that both height and BMI may play a role in the development of testicular cancer in men. The study highlighted the importance of considering both height and BMI as potential risk factors for testicular cancer. The findings supported previous research indicating a positive association between height and testicular cancer risk. The U-shaped relationship between BMI and testicular cancer risk was also emphasized, with underweight and obese men showing increased risks, suggests that both underweight and obese individuals may have an increased risk of developing testicular cancer compared to individuals with a normal BMI. This non-linear relationship indicates that extreme values of BMI, both low and high, may be associated with higher risks of testicular cancer. The study suggested that these factors may reflect underlying biological mechanisms related to cancer development. Additionally, the study discussed the implications of these findings for future research and the potential for interventions targeting modifiable risk factors such as BMI.**

Retrospective Cohort, OC: RR significant	https://sci-hub.se/10.3109/02841851003743077	24) Visceral abdominal obesity – is there an increased prevalence in men presenting with testicular teratoma? Lee Grant, 2010.	Retrospective cohort study. Population consisted of 22 male patients who had undergone staging CT between 2004 and 2007 for testicular teratoma. These patients were compared to a control group of 22 male patients matched for age, sex, and body mass index, selected from patients who had a normal CT examination following an acute episode of renal colic.	Obésité	2010	United Kingdom	Yes	Association between Visceral abdominal obesity and testicular teratoma	RR = 1,56 (CI: 1,08-2,2)	Yes	The study investigated the association between visceral abdominal obesity and testicular teratoma in male patients. The researchers compared abdominal adipose tissue distribution in 22 patients with testicular teratoma to 22 control patients matched for age, sex, and body mass index. The researchers compared the ratio of visceral to subcutaneous adipose tissue volumes between these two groups to assess the association between visceral abdominal obesity and testicular teratoma.They found that patients with testicular teratoma had a significantly higher ratio of visceral to subcutaneous adipose tissue volumes compared to the control group, with the ratio being 1.56 times greater in teratoma patients. This suggests that individuals with testicular teratoma have a relatively greater proportion of abdominal visceral adipose tissue. The study acknowledged limitations such as its retrospective design, the assumption of no confounding metabolic conditions, and the lack of baseline imaging for assessing changes in fat distribution with tumor presentation. Despite these limitations, the findings support the association between increased visceral adiposity and testicular teratoma. The authors suggested that the metabolic activity of visceral adipose tissue may play a role in the development of testicular teratoma. In conclusion, the study demonstrated a link between visceral abdominal obesity and testicular teratoma, highlighting the potential impact of adipose tissue distribution on cancer risk. Further research is needed to explore the underlying mechanisms and potential implications for cancer prevention and management.
Case-Control, OC: RR significant	https://sci-hub.se/10.1007/s00432-008-0504-1	25) Is increased body mass index associated with the incidence of testicular germ cell cancer? Dieckmann KP, 2008	Nationwide multicentric case-control study. Included a total of 8,498 patients with testicular germ cell cancer, compared to 2,070 age-matched male probands from the German National Health Survey.	Obésité	Germany, 2008, Klaus-Peter Dieckmann · Jörg Thomas Hartmann · Johannes Classen · Malte Diederichs · Uwe Pichlmeier	Germany	Yes	Association between BMI and Obesity and testicular cancer	($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls, for the age group of 18-29 years.	Yes	Statistical significance is achieved ($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls" for the age group of 18-29 years. This indicates that in young men aged 18-29 years, there was a statistically significant association between higher BMI categories and testicular germ cell cancer compared to controls. The data on body dimensions, including BMI, were self-reported by the participants. This self-reporting method may introduce bias and inaccuracies in the data, which could affect the reliability of calculating the OR. The study lacked complete data on other potential risk factors for testicular germ cell cancer. Without comprehensive information on all relevant risk factors, calculating a meaningful OR could be challenging and may lead to biased results. Due to the limitations in data quality and completeness, the researchers chose to conduct a descriptive analysis of BMI frequencies instead of calculating the OR, as a more appropriate and feasible approach given the available data Unfortunately, due to the limitations mentioned earlier, a formal calculation of odds ratios was not feasible in this study.

case-control, OC: RR NO SIGNIFICANT	https://sci-hub.yt/10.1002/ijc.2910430403	26) Testis Cancer: Post-Natal Hormonal Factors, Sexual Behaviour and Fertility. A.J. Swerdlow, 1989.	Case-control study. The study included 259 testis cancer cases and 2 sets of controls. Controls were men without testis cancer in the same area. Study to investigate the relationship between testis cancer risk and variables related to hormonal status, sexual behavior, and fertility.	Obésité	1989	United Kingdom	Yes	Association between Obesity, Height, age of puberty and other factors and testicular cancer.	RR = 1,83 (IC 95% : 0,83-4,05)	No significant	For obesity, the study found that the risk of testis cancer was raised for men with a high Quetelet's index of obesity as adults, but this increase was not statistically significant. The relative risk (RR) for obesity in relation to testis cancer was 1.83 (0.83-4.05). The study did not find a consistent association between testis cancer risk and age at puberty, need to shave, obesity, alcohol intake, animal fat intake, and sexual behavior. There was a significant excess of seminomas in very tall men, but no significant linear trend of risk with height. Testis cancer cases showed lower fertility than controls, but this was mainly due to the higher frequency of cryptorchidism among cases. Among non-cryptorchid subjects, there was no clear evidence of an association between infertility and testis cancer risk. The data and previous literature do not provide convincing evidence that testis cancer risk is related to hormone levels, sexual behavior, or infertility, except in cases of cryptorchidism. Direct measures of hormone levels may be desirable to assess risk more accurately, especially in special groups with hormonal abnormalities. While infertility is unlikely to be a major risk factor for testis cancer, further study is needed to explore the possibility of increased risk among non-cryptorchid infertile men, possibly through a cohort approach.
case-control, OC: RR NO SIGNIFICANT Data missing	https://pubmed.ncbi.nlm.nih.gov/12869410/	27) Body size at birth and adulthood and the risk for germ-cell testicular cancer Lorenzo Richiardi, 2003	Nested case-control study. 371 patients with testicular cancer, registered in the Swedish Cancer Registry between 1958 and 1996 and aged 20-54 years at diagnosis, and 1238 individually matched controls were identified. Information on adult body size at age 18 years was obtained for all subjects through the Military Service Conscription Register, whereas perinatal information was obtained through birth records at the subjects' respective maternity wards.	obésité	2003	Sweden	Yes	Association between adult BMI and height, weight and height of birth, and Germ Cell testicular cancer	No association between the risk for testicular cancer and body mass index was found.	Not available	Height was positively associated with testicular cancer risk, and the association persisted after taking into account perinatal characteristics. The adjusted odds ratio (OR) was 1.55 [95% confidence interval (CI), 1.10-2.17] for the third tertile of height as compared with the first. Long duration of gestation was negatively associated with testicular cancer risk [OR = 0.64 (95% CI, 0.45-0.91), post-term compared with term], whereas high birth weight appeared to increase the risk [OR = 1.35 (95% CI, 0.99-1.85)]. In conclusion, adult height and perinatal factors acted independently, suggesting that both the fetal life and the childhood and adolescence periods are windows of susceptibility to exposures that influence the risk for testicular cancer.
Discussion Retrospective Cohort: WRONG OC	https://sci-hub.yt/10.1016/j.clgc.2019.04.012	Body Mass Index and Outcomes in Germ-Cell. Tumors. Bradley A., 2019.	Retroscpective population-based cohort study. Electronic medical records for 1161 GCT patients treated at Dana-Farber Cancer Institute between 1997 and 2012 were reviewed.		2019, Bradley A. McGregor, Rowan E. Miller, Elizabeth O'Donnell, Laurence K. Albiges, Christopher J. Sweeney, Sarah C. Markt		Wrong OC	Association between BMI and therapeutic response to testicular cancer			

Type étude	N° zotero	Title. Main Author, Year of Publication	Study Type. Population. Comparator(s)	Type chaleur	Année, Authors	Pays	Lien O/N	Obj ppal	Obj p value	CCL O/N	Remarques
Case-control, OC: RR No significant	https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/1097-0142%28198504	13) Familial Testicular Cancer and Urogenital Developmental Anomalies. David J. TOLLERUD, 1985.	Case-control study. Newly diagnosed cases of testicular cancer referred to three participating hospitals from January 1976, through June 1981, and controls with similar characteristics of age, sex, and race selected from individuals with other forms of cancer hospitalized at the same institutions	hydrocele	1985; DAVID J. TOLLERUD, MD,' WILLIAM A. BLATTNER. MD,' MARY C. FRASER, RN. MA,' LINDA MORRIS BROWN, MPH,' LINDA POTTERN, MPH,' ELLEN SHAPIRO, MD,' AARON KIRKEMO, MD,' THOMAS H. SHAWKER, MD,' NASSER	USA	yes	Association between a familial history of hydrocele and familial testicular cancer	SIR: 1,3 (IC à 95%: 0,2-8,9)	no significant	*The several clusters of genitourinary malformations in families of men with testicular cancer, although the data we collected on this is insufficient for formal analysis, add to previous evidence suggesting that familial associations of testicular cancer and such malformations may sometimes have a genetic basis. The high prevalence of cryptorchidism, inguinal hernias, and hydroceles among men in these families suggests that an underlying alteration in urogenital embryogenesis may be associated with the familial predisposition to testicular neoplasia. The study focuses on the family history of urogenital anomalies in close relatives of patients with testicular cancer, such as inguinal hernia, cryptorchidism, varicocele, hydrocele, etc. It explores how these family histories may be related to the risk of developing testicular cancer. The study was a case-control study that examined the occurrence of testicular cancer and urogenital anomalies in family members. Six familial clusters with testicular cancer in first-degree relatives were identified. Urogenital abnormalities were reported more frequently in familial cases and close relatives compared to non-familial cases and their relatives, suggesting a heritable cancer-prone diathesis . 6 out of 269 testicular cancer cases (2.2%) had a first-degree relative with testicular cancer, compared to 1 out of 259 controls (0.4%) . Fathers and brothers of testicular cancer cases had a six-fold elevated risk of developing testicular malignancy compared to men in the general population . Cryptorchidism was reported in 17% of familial cases, 2.7% of controls, and 5.3% of cases with no family history of testicular cancer . The presence of cryptorchidism, inguinal hernias, and hydroceles among men in high-risk families suggests an association with an underlying alteration in urogenital embryogenesis linked to familial predisposition to testicular neoplasia*
Case-control, OC: RR No significant	https://sci-hub.se/10.1097/00001648-199601000-00004	6) Genital anomalies and risk for testicular cancer in Danish men. A Prener, 1996.	Case-control study. 183 cases of testicular cancer registered in the Danish Cancer Registry. For each case, 2 age- and sex-matched controls were selected, resulting in a total of 366 controls. . In a cohort of Danish boys characterized by (1) being born between 1941 and 1957, (2) having attended schools in a defined area of Denmark	hydrocele	1996 A Prener 1, G Engholm, O M Jensen	Denmark	yes	Association between urogenital anomalies and testicular cancer	RR = 2,4 (IC 95 % = 0,6-9,0)	no significant	In a cohort of Danish boys characterized by (1) being born between 1941 and 1957, (2) having attended schools in a defined area of Denmark, and (3) having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985. We selected 366 age- and sex-matched controls from the same cohort. Using information recorded by school physicians, we performed logistic regression analyses to estimate the relative risks (RR) associated with various genital anomalies. We found the risk for testicular cancer to be raised for men with a history of cryptorchidism [RR = 5.2; 95% confidence interval (CI) = 2.1-13.0], inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7), hypospadias (RR = 4.2; 95% CI = 0.4-42.7), and hydrocele (RR = 2.4; 95% CI = 0.6-9.0). We observed no decrease in the risk associated with cryptorchidism after correction of the maldescent in early childhood. The RR of testicular cancer in the contralateral, normally descended testis in unilateral cryptorchid men was increased to 3.6. The results add to the growing evidence for a common causal factor for both testicular cancer and cryptorchidism and support the findings from other studies of associations between other genital anomalies involving the closure of the processus vaginalis and the risk of testicular cancer.
Case-control, OC: RR No significant	https://sci-hub.se/10.1136/jech.36.2.96	7) Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. A.J. Swerdlow, 1982.	Case-control study based on 87 deaths from testicular cancer in children in Great Britain from 1953 to 1973. The cases were children who died from testicular cancer, while the controls were children who died from other causes.	hydrocele	1982	United Kingdom	yes	Association between urogenital anomalies and testicular cancer	RR = 2.99 ; p-value = 0.15	no significant	For inguinal hernia, the relative risk (RR) was 2.05 with a p-value >0.05, indicating no significant risk associated with inguinal hernia. For hydrocele, the RR was 2.99 with a p-value of 0.15, also suggesting no significant risk associated with hydrocele. It is important to note that these results did not show a significant association between these specific genitourinary anomalies and the risk of testicular cancer in children.

Type étude	N° zotero	Title, Main Author, Publication Year.	Study Type. Comparator(s).	Type chaleur	Année	Pays	Lien O/N	Obj ppal	Obj p value	CCL O/N	Remarques
Case-control Study, OC significant	file:///Users/leachenard/Desktop/Association%20between%20Testicular%20Cancer%20and%20Epididymoorchitis-	28) Association between Testicular Cancer and Epididymoorchitis: A Population-Based Case-Control Study. LI-Ting Kao, 2016	Population-based case-control study. The study population included 372 patients with testicular cancer and 3,720 age-matched controls without testicular cancer. The comparator was from from the Taiwan Longitudinal Health Insurance Database 2005.	inflammation	15/03/2016 , Li-Ting Kao1,2,*, Herng-Ching Lin2,*, Shiu-DongChung 2,3 & Chao-Yuan Huang	China	Yes	Association between testicular cancer and prior epididymoorchitis.	OR = 47,17 (IC 95% = 23,83 - 93,40)	Significant	The results of the study showed a significant association between testicular cancer and prior epididymoorchitis. The crude odds ratio for this association was 38.24 (95% CI: 19.91–73.46) , and after adjusting for potential confounders, the odds ratio remained significant at 47.17 (95% CI: 23.83–93.40) . Additionally, testicular microlithiasis was also found to be significantly associated with testicular cancer, with an adjusted odds ratio of 5.88 (95% CI: 2.77–12.48) . The study highlighted the importance of regular urological examinations for patients with a history of epididymoorchitis and suggested the need for further biological studies to understand the mechanisms underlying this association.
Case-control Study, OC significant	https://sci-hub.se/10.1038/sj.bjc.6690611	3) Risk factors for testicular germ cell tumours by histological tumour type. CAC Coupland, 1999.	Case-control study. Population: Men diagnosed with testicular germ cell tumors between 1 January 1984 and 30 September 1986, aged 15-49 years, and resident in the defined study areas Comparator: Each case was matched with a control selected from the list of the general practitioner with whom the case was registered, matched by date of birth to within 1 year.	inflammation	1999	UK	Yes	Association between a history of STD and testicular cancer	OR significant **for Non seminoma**: OR = 1,8 (CI 95%: 1-3,2)	Significant	In this , a history of sexually transmitted diseases (STDs) was associated with an increased risk of non-seminoma compared to pure seminoma tumors. The odds ratio (OR) for the association between a history of STDs and non-seminoma tumors was 1.8 (95% confidence interval [CI]: 1.0-3.2). This suggests that individuals with a history of STDs may have a higher risk of developing non-seminoma testicular germ cell tumors compared to those with pure seminoma tumors.
Case-control Study, OC significant	Full text non available	29) Mumps, orchitis and testicular germ cell tumors: A cause for concern? Trabert B. 2011.	Case-control Study. TGCT cases diagnosed between 2002 and 2005 (n = 767) were matched on age, race and serum draw date to at least one control (n = 929).	inflammation	2011	USA	Yes	Association between mumps, orchitis and testicular cancer (seminoma, non seminoma and TGCT)	**For TGCT** : Orchitis OR= 2.17 [95% CI: 1.37-3.46], Mumps [OR: 0.88, 95% CI: 0.63-1.23]. For Seminoma : Orchitis [OR: 1.65, 95% CI: 0.94-2.90], Mumps [OR: 0.79, 95% CI: 0.52-1.20]. **For Nonseminoma** : Orchitis OR 2.50 [95% CI: 1.43-4.38], Mumps [OR: 1.22, 95% CI: 0.81-1.84].	Significant	Orchitis was associated with a 2.17-fold increased risk of TGCT [95% CI: 1.37-3.46], while mumps did not show a significant association with TGCT risk [OR: 0.88, 95% CI: 0.63-1.23]. For seminoma, neither mumps [OR: 0.79, 95% CI: 0.52-1.20] nor orchitis [OR: 1.65, 95% CI: 0.94-2.90] were identified as risk factors. In the case of nonseminoma, orchitis was associated with a 2.50-fold increased risk [95% CI: 1.43-4.38], while mumps did not show a significant association [OR: 1.22, 95% CI: 0.81-1.84]. These findings suggest a potential link between orchitis and TGCT risk, particularly in the nonseminoma subgroup.

Case-control Study, OC significant	https://sci-hub.se/10.1038/bjc.1987.20	10) Testicular cancer and antecedent diseases. A.J. Swerdlow, 1987.	Case-control study Population studied: 259 cases of testicular cancer, 238 men with other diagnoses attending the same radiotherapy centers as the cases, and 251 hospitalized patients not attending radiotherapy services. Comparators: Two control groups - men with other diagnoses attending the same radiotherapy centers as the cases, and hospitalized patients not attending radiotherapy services.	inflammation	1987	UK	Yes	Association between inguinal hernia, mumps orchitis, infection and testicular cancer.	Mumps orchitis : RR = 12.7 (p = 0.006)	Significant	The case-control study on the etiology of testicular cancer conducted by Swerdlow et al. (1987) involved 259 cases of testicular cancer, 238 men with other diagnoses, and 251 hospitalized patients. The study found an increased risk of testicular cancer associated with a history of mumps orchitis (RR = 12.7, p = 0.006) and atopy (RR = 1.8, p = 0.03). Discussion: The study results underscore the importance of considering factors such as mumps orchitis and atopy in assessing the risk of testicular cancer. The challenges in accurately determining past medical history, especially in cryptorchidism cases, highlight the need for more robust study designs like cohort studies. The discussion also addresses the potential confounding factors related to inguinal hernia and undescended testis, emphasizing the need for further research to elucidate the mechanisms underlying the observed associations.
Case-control Study, OC NO significant	https://sci-hub.se/10.1038/bjc.2012.45	30) Childhood infections, orchitis and testicular germ cell tumours. Trabert B, 2012.	Case-control Study. The Comparators were Controls were drawn from the same well-defined population.	inflammation	2012	USA	Yes	relationship between common infections and TGCT risk.	OR of 1.80 (95% CI: 0.74 – 4.42)	NO SIGNIFICANT	For mumps: The pooled summary odds ratio (OR) based on the random-effects model was 1.03 (95% CI: 0.89 – 1.20), indicating no significant association with TGCT risk. The analysis showed very little heterogeneity among the six studies, with an I2 value of 6.1% (indicating low heterogeneity). For mumps orchitis or orchitis: The random-effects model produced a pooled OR of 1.80 (95% CI: 0.74 – 4.42) for the association with TGCT risk. There was considerable heterogeneity across study-specific ORs, with an I2 value of 69.0% (suggesting high heterogeneity). Sensitivity analyses indicated that two recent studies contributed most to the heterogeneity. When these studies were removed, the heterogeneity decreased significantly (I2 = 0.0%) and the pooled ORs for fixed- and random-effects models became more consistent. These results suggest that while mumps did not show a significant association with TGCT risk, mumps orchitis or orchitis had a more varied impact across studies, with some studies indicating an increased risk.

Case-control Study, OC NO significant	https://sci-hub.yt/10.1136/jech.41.4.349	12) Testicular cancer in young men: the search for causes of the epidemic increase in the United States. Linda Morris Brown, 1987.	Case-control study. The study population included 271 men with testicular cancer and 259 controls in the Washington, DC area. Cases were men aged 18-42 who were newly diagnosed with testicular cancer between January 1976 and June 1981 and were referred to three collaborating medical centers in the Washington, DC area. Controls were selected from the same geographical area. as the cases, allowing for the comparison of various factors between the two groups to assess potential associations with testicular cancer risk.	inflammation	1987	USA	Yes	association between a history of mumps orchitis, orchitis and testicular malignancies	Mumps Orchitis RR = 5,8 (IC 95%: 0,7-129,7)	NO SIGNIFICANT	The study investigated various factors potentially related to the risk of testicular cancer in young men and aimed to evaluate if any of these factors could explain the significant increases in testicular cancer incidence over time. Factors such as sociodemographic characteristics, childhood residence, religion, and external factors affecting testicular temperature were examined. The study found a slight excess risk for individuals spending their childhood in urban areas compared to rural areas. While there was an apparent excess of Mormons with testicular cancer, it was not statistically significant. External factors like the type of underwear worn or bathing habits did not show significant differences between cases and controls. Additionally, individuals with undescended testis were found to be at an increased risk for developing testicular cancer. However, the association between mumps orchitis and testicular cancer was not statistically significant. Overall, the study did not find clear associations between these factors and the risk of testicular cancer, highlighting the complexity of potential risk factors for this type of cancer . The study used a case-control design to assess the associations between various factors and testicular cancer risk. The relative risk (RR) was approximated by the odds ratio, and 95% confidence intervals (CI) were calculated for the estimates. Factors like undescended testis and groin hernia were explored, with undescended testis showing a significantly elevated risk for testicular cancer. Other medical conditions and histories like mumps orchitis, allergies, and specific treatments were also examined, with varying levels of association with testicular cancer risk. The study did not find significant associations between testicular cancer risk and factors like specific allergies or bathing habits. These findings contribute to the understanding of potential risk factors for testicular cancer in young men. For mumps orchitis and testicular cancer, the study reported a positive but non-significant association, with mumps orchitis being reported for six cases and one control. However, the method of questioning subjects about a history of mumps and potential recall bias, as well as the difficulty in distinguishing mumps orchitis from other testicular conditions, may have influenced the results.
Cohort. OC: NO significant.	https://sci-hub.se/10.1007/s00404-011-1938-2	31) Incidence of testicular malignancies and correlation to risk factors in a TESE population of subfertile men. Banz-Jansen, 2011.	Retrospective Cohort study: 302 patient files of subfertile men who underwent testicular biopsies for TESE procedures between January 1995 and December 2004.	inflammation	2011, Constanze Banz-Jansen • Christoph Nikorowitsch • Thomas Drechsler • Ricardo Felberbaum • Andreas Schmutzler • Klaus Diedrich • Dominique Finas	Germany	Yes	association between a history of mumps orchitis and testicular malignancies	Mumps orchitis occurred among 20% of patients with testicular tumors .	NO SIGNIFICANT	Main objective of the study was to evaluate the incidence of testicular malignancies and risk factors in the subfertile male population treated with TESE in Northern Germany. These results suggest a potential association between a history of mumps orchitis and testicular malignancies in the studied population, but statistical results were not precised, and not significant.
Cohort. OC: NO significant.	https://sci-hub.se/10.1136/bmj.2.6080.191-a	32) Mumps orchitis and testicular tumours. W. Ehrengut, 1977.	Retrospective cohort study Population: Patients with testicular tumors in Hamburg, comparator was the total cohort population.	inflammation		Germany	Yes	association between a history of mumps orchitis, orchitis and testicular malignancies	not available	Yes	This Retrospective cohort study included Patients with testicular tumors in Hamburg, comparator was the total cohort population. The study focused on patients with testicular tumors and their history of mumps orchitis and epididymitis. The findings revealed a low occurrence of mumps orchitis in the past medical history of patients with testicular neoplasms. However, a significant proportion of patients with testicular tumors had a history of epididymitis on the affected side, suggesting a potential association. The study did not find any cases of testicular tumors among patients previously treated for mumps orchitis.

Analyse qualitative (complète) résultats non significatifs :

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

Cryptorchidism :

As stated earlier, during our research, we did not find any studies with focused results on the role of heat caused by cryptorchidism and its relation to testicular cancer. However, it seemed relevant for us to analyze in parallel the results of two studies that focused on the association between elevated intrascrotal heat in cryptorchidism and infertility, and the association between the pathophysiology of cryptorchidism and other urogenital malformations, and testicular cancer.

"Clinical and biological characteristics of infertile men with a history of cryptorchidism" by R. Mieusset. This case-control study confirmed that a history of cryptorchidism is a risk factor for fertility issues. It highlighted that the prevalence of cryptorchidism was significantly higher in infertile men compared to fertile men, emphasizing the negative impact of cryptorchidism on subsequent fertility. The findings also revealed new insights into the relationship between testis location, scrotal thermal state, and infertility in men with a history of cryptorchidism. The study suggested that scrotal hyperthermia due to cryptorchidism could have deleterious effects on spermatogenesis, leading to impaired fertility outcomes.

These results demonstrate the associations between scrotal heat due to cryptorchidism and characteristics such as retractile testes and high location of testis in infertile men with a history of cryptorchidism.The study addressed the link between scrotal heat and infertility in men with a history of cryptorchidism.

The results showed that 45% of infertile men with a history of cryptorchidism had abnormally high scrotal temperatures. The mean scrotal temperatures of the cryptorchid infertile men were significantly higher than those of the fertile men.

This temperature increase was associated with a more severely impaired spermatogenesis and a higher incidence of primary infertility compared to infertile men with a history of cryptorchidism but normal scrotal temperatures.

Additionally, it was found that men with scrotal hyperthermia had smaller testicular volumes and lower sperm production than those with normal scrotal temperatures.

Such an increase was previously reported in eight men with a testis located in the inguinal canal (Kitayama, 1965), and in 19 infertile men with a history of cryptorchidism (Carizza and al., 1990) ; however, the latter authors failed to find any significant difference from the scrotal temperature of fertile men, probably because of the restricted number of men.

Association of scrotal hyperthermia and a history of cryptorchidism does have a deleterious effect on spermatogenesis, since cryptorchid infertile men with scrotal hyperthermia have smaller testicular volumes and lower sperm output than cryptorchid infertile men with normal scrotal temperatures.

However, it is not known whether the elevated scrotal temperatures are a consequence of or are independent of cryptorchidism. Since elevated scrotal temperatures were previously

reported to be linked to testicular atrophy (Zorgniotti and MacLeod, 1973), this study seemed to conclude that the temperature rise may be the result of testicular atrophy, possibly due to unchanged blood flow with diminished testis parenchyma, or it may be due to cryptorchidism. The information provided by the present study does not prove that cryptorchidism is the cause of elevated temperatures.

Another study looked at cryptorchidism and its pathophysiology : **1) Testicular Cancer Risk Among Young Men : Role of Cryptorchidism and Inguinal Hernia.** By Linda M. Pottern, aimed to investigate the relationship between undescended testis and the risk of testicular cancer among young men.

The study mentioned that among individuals with unilateral cryptorchidism, the risk of testicular cancer was six times higher (CI = 1.9-23.5) for the ipsilateral testis and not elevated (CI = 0.1-7.0) for the contralateral testis. This means that the risk of testicular cancer was higher on the side where the undescended testis was located. And adjusted Risk Ratios for testicular cancer in the ipsilateral testis, elevated to 10.3 (CI = 3.4-36.8) when 8 bilateral cryptorchidism were included in the risk calculation. These results suggest a correlation between the side of the testicular tumor and the side of the cryptorchidism.

The study found a significant association between a history of cryptorchidism and testicular cancer, with a threefold increased risk for men who had undergone orchiopexy (surgical correction of undescended testis). The risk of testicular cancer was observed to increase with age at correction of cryptorchidism, indicating a direct relationship between the age of corrective surgery and cancer risk. These findings support the recommendation for early surgical correction of cryptorchidism to reduce the risk of testicular cancer. Indeed, early diagnosis and treatment of cryptorchidism are crucial to prevent long-term effects on germ cell development and fertility. It is recommended that orchidopexy (surgical fixation of the undescended testis) be performed before the age of 3 years to minimize germ cell loss and optimize future fertility outcomes.

Furthermore, the study also revealed a lack of elevation in risk for the contralateral testis, suggesting that internal factors affecting the retained testis in the body may be responsible for the increased cancer risk, rather than a congenital predisposition.

Overall, the study highlighted the potential role of increased testicular temperature or other exposures related to the presence of an undescended testis in the body in contributing to the elevated risk of testicular cancer.

On the contrary, as explained, the Mieusset and al.‘s study, does not seem to highlight a direct link between heat and cryptorchidism, and indeed concludes that temperature rise may be the result of testicular atrophy, possibly due to unchanged blood flow. The information provided by the study does not prove that cryptorchidism is the cause of elevated temperatures. This

conclusion needs to be nuanced, given the potential conflict of interest, as Dr. Mieusset developed the "contraceptiv slip", one of the first thermal contraceptive methods.

Indeed, about 10% of all cases of germ cell tumors occur in men with a history of cryptorchidism with the most accredited hypothesis related to the elevated temperature of the undescended testis, thus inhibiting the differentiation of spermatogonia and resulting in an arrest of spermatogenesis, germ cell depletion, and fibrosis. (55).
In addition, the altered position of the testis could alter the function of the somatic cells forming the niche for spermatogonial stem cells' self-renewal and differentiation. The histological dysgenetic changes in testicles with cancer may be due to abnormalities in the fetal development of germ cells. Testicular germ cell cancer is presumed to derive from carcinoma in situ (CIS) cells that originate from primordial germ cells escaping normal differentiation during fetal development. These CIS cells are considered the precursor of all types of germ cell tumors, except spermatocytoma. Therefore, the dysgenetic changes observed in the histology of testicles in patients with testicular cancer could result from these cellular developmental alterations during the fetal period.

The overall risk of developing testicular cancer in patients who were or are cryptorchid is 3.7–7.5 times higher than in the normal population (56)(57). Although corrective surgery diminishes this risk by half, the former cryptorchid testis becoming cancerous indicates that permanent epigenetic changes are reported in the testis (58). Recent evidence suggests that allelic variants in genes implicated in the development of the testes could be present in a patient with cryptorchidism. In particular, KIT gene variants might be the determinants in the association between this condition and testicular cancer (59). However, up to now, even if an irrefutable higher risk of testicular cancer in patients affected by previous or current cryptorchidism has been found, the real pathogenetic mechanism underlying this association is still unclear (60).

Previous investigators have reported that premalignant changes in the form of abnormal germ cells can be detected in the cryptorchid and infertile adult testis (61).

These cells are characterized by a thin rim of pale-staining cytoplasm, a large hyper chromatic nucleus and prominent nucleoli. 113 biopsies from 102 patients were studied, to determine if these abnormal germ cells occur in the nonadult cryptorchid testis. The patients ranged in age from 3 months to 16 years. Evaluation of testicular tissue disclosed histological alterations in the undescended testis, which were those commonly ascribed to the undescended testis. However, none of the changes could be interpreted as premalignant. The abnormal germ cells described by other investigators were not found in any of these specimens.(62)

Regarding scrotal heat exposure, it can also play a role in the histological changes observed in testicles with cancer. Studies have demonstrated that exposure to high temperatures, such as those induced by cryptorchidism or other conditions increasing scrotal heat, can negatively impact spermatogenesis and germ cell health, thereby elevating the risk of testicular cancer. Thus, in addition to fetal developmental cellular alterations, scrotal heat seems to also contribute to the histological changes seen in testicles associated with testicular cancer.

Inguinal Hernia :

11) Testicular cancer in young men : the search for causes of the epidemic increase in the United States. Linda Morris Brown, 1987.

This study used a case-control design to assess the associations between various factors and testicular cancer risk. It investigated various factors potentially related to the risk of testicular cancer in young men and aimed to evaluate if any of these factors could explain the significant increases in testicular cancer incidence over time. Factors such as sociodemographic characteristics, childhood residence, religion, and external factors affecting testicular temperature were examined. The study found a slight excess risk for individuals spending their childhood in urban areas compared to rural areas. While there was an apparent excess of Mormons with testicular cancer, it was not statistically significant. External factors like the type of underwear worn or bathing habits did not show significant differences between cases and controls. Factors like undescended testis and groin hernia were explored, with undescended testis showing a significantly elevated risk for testicular cancer. Other medical conditions and histories like mumps orchitis, allergies, and specific treatments were also examined, with varying levels of association with testicular cancer risk. The study did not find significant associations between testicular cancer risk and factors like specific allergies or bathing habits. Additionally, individuals with undescended testis were found to be at an increased risk for developing testicular cancer. Regarding a history of hernia and testicular cancer, the study did not find a substantial risk associated with a history of groin hernia operation. This lack of significant association suggests that a history of hernia may not be a strong risk factor for testicular cancer in the studied population. For mumps orchitis and testicular cancer, the study reported a positive but non-significant association, with mumps orchitis being reported for six cases and one control. However, the method of questioning subjects about a history of mumps and potential recall bias, as well as the difficulty in distinguishing mumps orchitis from other testicular conditions, may have influenced the results.

Overall, the study did not find clear associations between these factors and the risk of testicular cancer, highlighting the complexity of potential risk factors for this type of cancer.

These findings contribute to the understanding of potential risk factors for testicular cancer in young men.

13) Congenital anomalies in children with testicular germ cell tumor. Shiego Sakashita, 1980. This study retrospectively analyzed 25 patients with testicular germ cell tumors, including 20 cases of yolk sac tumors and 5 cases of teratomas. Among these patients, congenital anomalies were observed in 3 individuals with yolk sac tumors and 1 individual with a mature teratoma. The identified abnormalities included a retrocaval ureter, diverticulum of the bladder, Down's syndrome, and an ipsilateral inguinal hernia. In the study, it was observed that among the 25 children with testicular germ cell tumors, 4 patients (16%) had associated congenital malformations. Among these anomalies, inguinal hernia was the most common, with an estimated incidence of 10% among children with testicular tumors. The results suggest that

there may be a link between tumor development and the presence of congenital anomalies in children with testicular tumors. Therefore, it is recommended to carefully examine young patients with testicular tumors for potential congenital abnormalities. The study highlighted the differences in etiology, pathology, and clinical features of pediatric testicular germ cell tumors compared to adult cases. The predominant tumors in children were teratomas and yolk sac tumors, with a better prognosis in children than in adults. The study suggested that the oncogenesis of testicular tumors in infants may begin in utero.

14) Familial Testicular Cancer in a Single-centre Population. D.J.A. Sonneveld, 1999. The study retrospectively analyzed familial testicular cancer cases in a single-center population of 693 patients treated between 1977 and 1997. It aimed to assess the proportion of familial testicular cancer cases and estimate the relative risk for first-degree relatives of patients. Additionally, the study evaluated the occurrence of bilateral testicular neoplasms and urogenital developmental anomalies in families with a predisposition to testicular cancer. The results showed that 3.5% of patients had a first-degree relative with testicular cancer, with a total of 24 familial cases belonging to 17 families. The study highlighted the presence of inguinal hernias in 8% of familial cases with affected first-degree relatives. Results regarding inguinal hernia from the study are as follows: 3 patients (8.3%) with familial testicular cancer had a history of inguinal hernia. In familial cases with affected first-degree relatives, inguinal hernias were present in 8% of cases. The study found that the proportion of urogenital developmental anomalies, such as undescended testis (UDT) and inguinal hernias, was slightly higher in familial testicular cancer cases compared to historical general testicular cancer cases. However, these figures were not significantly different from non-familial cases reported in the literature. The presence of UDT in 17% of testicular cancer cases with affected second- or third-degree relatives suggests an association between UDT and familial occurrence of testicular cancer. It is noted that there may be bias in ascertainment due to over-reporting of relatives with these anomalies.

15) Occurrence of testicular cancer in patients operated on for cryptorchidism and inguinal hernia. Pinczowski, 1991. Studied the incidence of testicular cancer in 2 population-based cohorts involving 2,918 men who underwent an operation for a cryptorchid testis and 30,199 who underwent surgery for an inguinal hernia. Complete followup during the 19-year period was achieved by record linkage to the National Swedish Cancer Registry. In the cryptorchidism cohort 4 cases of testicular cancer occurred versus 0.54 expected, yielding a RR of 7.4 (95% CI 2.0 to 19.0). Of these patients 3 had undergone a bilateral operation due to intra-abdominal testes. There was no evidence of an association between inguinal hernia and risk of testicular cancer (RR = 1.1, 95% CI= 0.4 to 2.2). The validity of data was further supported by relative risk estimates close to unity in a comparison group of appendectomy patients. They conclude that patients with a cryptorchid testis experience a substantially increased relative risk of testicular cancer. However, the low absolute risk, 4 cases during 25,360 person-years of observation, does not appear to justify special surveillance after an operation for an undescended testis.

16) The Relation Between Testicular Tumours, Undescended Testes, and Inguinal Hernias. Th. Wobbes, 1980. In this cohort study, an inguinal hernia was found in 3.4% of the patients with a testicular tumour. Consequently, there seems to be no increased risk for patients with a history of an operation for inguinal hernia. In the study, it was reported that the risk of malignancy in an undescended testis proved to be about 17 times greater than in the normal population. Regarding inguinal hernia, no increased risk was found for patients with a history of inguinal hernia.

Varicocele:

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

The study investigated the potential link between elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men.

No significant association was found between testicular cancer and wearing tight-fitting underwear or heat-resistant clothing at work.

A slightly higher proportion of men with testicular cancer reported wearing long underwear for more than three months per year compared to controls.

Controls reported more use of hot tubs or saunas than men with testicular cancer.

A slightly higher proportion of men with testicular cancer had a history of physician-diagnosed varicocele.

The study did not provide strong support for the hypothesis that intermittent intrascrotal temperature elevation contributes to the development of testicular cancer.

Previous research has shown that increased intrascrotal temperature can affect spermatogenesis and sperm morphology.

Further evaluation is needed to determine if continuous temperature elevation, such as that seen in varicocele, may increase the risk of testicular cancer.

These findings suggest that while there may be some associations between intrascrotal temperature and testicular cancer, more research is required to fully understand the potential mechanisms involved.

18) Varicocoele in adolescence and testicular cancer in young adulthood. Guy Verhovsky, 2022.

Elevated intrascrotal temperature has been suggested as a risk factor for testicular cancer, which is the most common neoplasm among young men. Varicocoele was linked to increased intrascrotal temperature, but whether it is associated with testicular cancer is unclear. To explore the possible association between varicocoele at adolescence and the incidence of testicular cancer at adulthood, this nationwide, population-based, historical cohort study includes 1,521,661 Israeli male adolescents (mean age 17.5 ± 0.4 years), who were screened for varicocoele during the years 1967-2012, as part of their medical assessment prior to compulsory military service. The mean follow-up was 18 ± 4.2 years. The diagnosis of testicular cancer was ascertained from linkage of records to the the Israeli National Cancer Registry. In total, 53,210 adolescents were diagnosed with varicocoele stages 2 and 3 prior to military service. Of 1988 (0.13% of the total cohort) men who were diagnosed with testicular cancer during follow-up, 54 (0.1%) had varicocoele prior to military service, while 1934 (99.9%) did not, p = 0.213. The mean age at diagnosis of testicular cancer and the distribution of seminomas versus non-seminomas did not differ significantly between the two groups. In a multivariable analysis controlling for sociodemographic factors, varicocoele was not associated with testicular cancer, OR = 0.816 (CI: 0.615-1.083). They found no association between varicocoele in young adulthood and testicular cancer later in life.

The completion of 12 years of schooling was more common among adolescents with varicocoele, suggesting a potential socioeconomic factor.

The study highlights the importance of considering various factors such as education and socioeconomic status in understanding the relationship between varicocoele and testicular cancer. Healthcare providers should be aware of these findings when assessing and counseling adolescents with varicocoele regarding their long-term health risks. These results contribute to the existing knowledge on varicocoele and testicular cancer risk, emphasizing the need for further research to explore the complex interplay of factors influencing the development of testicular cancer in young adults.

Obesity:

19) Worldwide Distribution, Risk Factors, and Temporal Trends of Testicular Cancer Incidence and Mortality: A Global Analysis. Huang J, 2011.

There was a wide variation in the testicular cancer burden with the highest mortality found in low-income countries, and the regions of Central America and South America, while the highest incidence was observed in high-income countries, especially in Western and Northern Europe. They found a positive association for HDI, GDP, alcohol drinking, inactivity, overweight,

obesity, and hypercholesterolaemia with testicular cancer incidence, while a negative correlation was observed between GDP and mortality of testicular cancer. Globally, there was an overall increasing incidence trend of testicular cancer for the past decade, particularly in younger males; the mortality trends of testicular cancer were relatively stable. Globally, testicular cancer incidence had been increasing particularly in the younger population, although its deaths rates had been decreasing. Socioeconomic indices, alcohol drinking, inactivity, overweight, obesity, and high plasma lipid levels are associated with testicular cancer incidence and mortality. However, they did not analyse the trend of different stages and subtypes of testicular cancer due to data unavailability.

20) Regional variations in testicular cancer rates in Ireland. M. Alsinnawi, 2010.

This study aimed to investigate the incidence of testicular cancer (TCa) in different counties of Ireland between 1994 and 2007. The researchers also explored potential factors such as cryptorchidism, socio-economic status, environmental pollutants, and teenage obesity as risk factors for the development of testicular cancer.

Cork County had a significantly higher rate of testicular cancer compared to other counties in Ireland. While high rates of cryptorchidism were observed in Cork, they alone could not explain the elevated incidence of testicular cancer.

Areas with higher socio-economic status in Cork showed significantly higher rates of testicular cancer. Organic pollutants linked to testicular cancer were identified in industries located only in Cork.

Teenage obesity rates in Cork were not higher than in other regions. Despite analyzing teenage obesity data as a potential risk factor for testicular cancer, the study did not find a significant association between obesity and testicular cancer incidence. The distribution of obesity among adolescents in different regions of Ireland did not align with the regional variations in testicular cancer rates. This suggests that factors other than obesity may play a more significant role in explaining the observed differences in testicular cancer incidence across counties.

21) Body size and cancer of the testis.T.W.Davies, 1990.

This study analyzed data from 438 cases of testicular cancer and their controls, investigating the relationship between body size and testicular cancer incidence. The analysis included logistic regression models and categorized body measurements (height, weight, and body mass index) as factors. The study found no systematic statistically significant differences in body measurements between cases and controls. Interestingly, the future victims of testicular cancer were observed to be lighter, smaller, and thinner than unaffected controls, particularly in the younger age group. The difference between cases and controls diminished with increasing age, suggesting that weight gain during adolescence might be a promotional factor for testicular cancer. The study also noted that the social class distribution of cases did not differ significantly

from the general population in Denmark. The study did not confirm the initial hypothesis that high fat or calorie intake leading to relative obesity could be a promotional factor for testicular cancer. Instead, the findings indicated a trend where individuals who later developed testicular cancer were lighter, smaller, and thinner than unaffected controls. The authors emphasized the importance of considering body size factors in the context of testicular cancer risk, highlighting the need for further research to understand the complex relationship between body size and cancer development. Additionally, the study noted that the social class distribution of testicular cancer cases in Denmark did not align with findings from other studies associating testicular cancer with higher social class, suggesting potential environmental and lifestyle factors at play in different populations.

25) Testis Cancer : Post-Natal Hormonal Factors, Sexual Behaviour and Fertility. A.J. Swerdlow, 1989.

For obesity, the study found that the risk of testis cancer was raised for men with a high Quetelet's index of obesity as adults, but this increase was not statistically significant. The relative risk (RR) for obesity in relation to testis cancer was 1.83 (0.83-4.05). The study did not find a consistent association between testis cancer risk and age at puberty, need to shave, obesity, alcohol intake, animal fat intake, and sexual behavior.

There was a significant excess of seminomas in very tall men, but no significant linear trend of risk with height. Testis cancer cases showed lower fertility than controls, but this was mainly due to the higher frequency of cryptorchidism among cases.

Among non-cryptorchid subjects, there was no clear evidence of an association between infertility and testis cancer risk.

The data and previous literature do not provide convincing evidence that testis cancer risk is related to hormone levels, sexual behavior, or infertility, except in cases of cryptorchidism. Direct measures of hormone levels may be desirable to assess risk more accurately, especially in special groups with hormonal abnormalities.

While infertility is unlikely to be a major risk factor for testis cancer, further study is needed to explore the possibility of increased risk among non-cryptorchid infertile men, possibly through a cohort approach.

26) Body size at birth and adulthood and the risk for germ-cell testicular cancer

Lorenzo Richiardi, 2003.

Height was positively associated with testicular cancer risk, and the association persisted after taking into account perinatal characteristics. The adjusted odds ratio (OR) was 1.55 [95% confidence interval (CI), 1.10-2.17] for the third tertile of height as compared with the first. Long duration of gestation was negatively associated with testicular cancer risk [OR = 0.64

(95% CI, 0.45-0.91), post-term compared with term], whereas high birth weight appeared to increase the risk [OR = 1.35 (95% CI, 0.99-1.85)]. In conclusion, adult height and perinatal factors acted independently, suggesting that both the fetal life and the childhood and adolescence periods are windows of susceptibility to exposures that influence the risk for testicular cancer.

Hydrocele:

5) Genital anomalies and risk for testicular cancer in Danish men. A Prener, 1996.

In a cohort of Danish boys characterized by being born between 1941 and 1957, having attended schools in a defined area of Denmark, and having a school health record available, 183 were registered in the Danish Cancer Registry with testicular cancer diagnosed before January 1, 1985. 366 age- and sex-matched controls from the same cohort were selected. Using information recorded by school physicians, the relative risks (RR) associated with various genital anomalies was estimated. They found the risk for testicular cancer to be raised for men with a history of cryptorchidism [RR = 5.2; 95% confidence interval (CI) = 2.1-13.0], inguinal hernia (RR = 1.8; 95% CI = 0.9-3.7), hypospadias (RR = 4.2; 95% CI = 0.4-42.7), and hydrocele (RR = 2.4; 95% CI = 0.6-9.0). They observed no decrease in the risk associated with cryptorchidism after correction of the maldescent in early childhood. The RR of testicular cancer in the contralateral, normally descended testis in unilateral cryptorchid men was increased to 3,6. The study seems to highlight a common causal factor for both testicular cancer and cryptorchidism and support the findings from other studies of associations between hydrocele and other genital anomalies involving the closure of the processus vaginalis and the risk of testicular cancer.

6) Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953-73. A.J. Swerdlow, 1982.

In this case-control study, for inguinal hernia, the relative risk (RR) was 2.05 with a p-value >0.05, indicating no significant risk associated with inguinal hernia.

For hydrocele, the RR was 2.99 with a p-value of 0.15, also suggesting no significant risk associated with testicular cancer and hydrocele (RR = 2.4; 95% CI = 0.6-9.0).

It is important to note that these results did not show a significant association between these specific genitourinary anomalies and the risk of testicular cancer in children.

Orchitis, epididymitis, and testicular inflammation :

29) Childhood infections, orchitis and testicular germ cell tumours. Trabert B, 2012.

This analysis mumps and mumps orchitis in relation to testicular germ cell tumor (TGCT) risk yielded the following results: For mumps:

The pooled summary odds ratio (OR) based on the random-effects model was 1.03 (95% CI: 0.89 – 1.20), indicating no significant association with TGCT risk.

The analysis showed very little heterogeneity among the six studies, with an I2 value of 6.1% (indicating low heterogeneity). For mumps orchitis or orchitis:

The random-effects model produced a pooled OR of 1.80 (95% CI: 0.74 – 4.42) for the association with TGCT risk.

There was considerable heterogeneity across study-specific ORs, with an I2 value of 69.0% (suggesting high heterogeneity).

Sensitivity analyses indicated that two recent studies contributed most to the heterogeneity.

When these studies were removed, the heterogeneity decreased significantly (I2 = 0.0%) and the pooled ORs for fixed- and random-effects models became more consistent.

These results suggest that while mumps did not show a significant association with TGCT risk, mumps orchitis or orchitis had a more varied impact depending on other factors.

30) Incidence of testicular malignancies and correlation to risk factors in a TESE population of subfertile men. Banz-Jansen, 2011.

This Retrospective Cohort study, included 302 patient files of subfertile men who underwent testicular biopsies for TESE procedures between January 1995 and December 2004. The comparator was the total cohort. The main objective of the study was to evaluate the incidence of testicular malignancies and risk factors in the subfertile male population treated with TESE in Northern Germany. These results suggest a potential association between a history of mumps orchitis and testicular malignancies in the studied population.

31) Mumps orchitis and testicular tumours. W. Ehrengut, 1977.

This Retrospective cohort study included Patients with testicular tumors in Hamburg, comparator was the total cohort population. The study focused on patients with testicular tumors and their history of mumps orchitis and epididymitis. The findings revealed a low occurrence of mumps orchitis in the past medical history of patients with testicular neoplasms. However, a significant proportion of patients with testicular tumors had a history

VI. RESUME ET MOTS CLES

1. ABSTRACT

Are intracorporeal body sources of heat a risk for testicular cancer, a systematic review

Introduction: Testicular cancer is the most common solid malignancy cancers among young 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 internal and endogenous heat exposures. The population was composed of men without age criteria and the comparator was the general male population. A narrative analysis was made.

The protocol was registered on PROSPERO on 17/09/2023 with the following **ID: CRD42023464097.**

Results: 31 original articles selected from 2765 articles eligible for analysis. Results from narrative analyses: Regarding the role of heat caused by cryptorchidism in testicular carcinogenesis, studies have not shown any significant link. Inguinal hernia showed positive association with testicular cancer. Results suggest a potential association between inguinal hernia and an increased risk of testicular germ cell tumors, particularly for certain histological types. Regarding the association between varicocele and testicular cancer, unfortunately, we did not find any significant results. For obesity, visceral abdominal obesity showed significant positive association with testicular teratoma, highlighting the potential impact of adipose tissue distribution on cancer risk, and Higher BMIs seemed to be positively associated with testicular seminomas. Regarding the association between hydrocele and testicular cancer, unfortunately, we did not find any significant results. Regarding orchitis, epididymitis and genital infections, non-seminomas seemed to be positively associated with orchitis, epididymitis, mumps orchitis, and sexual transmitted diseases.

Discussion: This study can only hypothesis that there may be a link between testicular cancer and intra-scrotal and endogenous source of heat (only for inguinal hernia, obesity and prior uro-genital infections). Inguinal hernia and obesity being contraindications to the use of thermal contraception. However, with regard to the factors of obesity and genital infections, these results should be interpreted with caution in the light of the influence of other conditions and associated factors, and the conclusions of new, more recent meta-analyses.

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

2. RÉSUMÉ

La chaleur d'origine intra-corporelle constitue-t-elle un risque de cancer testiculaire ? Revue systématique de la littérature

Introduction : Le cancer du testicule est la tumeur solide la plus fréquente chez l'homme jeune. L'analyse 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 interne. La population était composée des hommes sans critère d'âge et le comparateur était la population masculine générale. 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 : 31 articles originaux ont été sélectionnés parmi 2765 articles éligibles à l'analyse.

Résultats de l'analyse narrative : En ce qui concerne le rôle de la chaleur causée par la cryptorchidie dans la carcinogenèse testiculaire, les études n'ont pas montré de lien significatif. La hernie inguinale a montré une association positive avec le cancer du testicule. Les résultats suggèrent une association potentielle entre la hernie inguinale et un risque accru de tumeurs germinales testiculaires, en particulier pour certains types histologiques. En ce qui concerne l'association entre la varicocèle et le cancer du testicule, nous n'avons malheureusement pas trouvé de résultats significatifs. En ce qui concerne l'obésité, l'obésité abdominale viscérale a montré une association positive significative avec le tératome testiculaire, soulignant l'impact potentiel de la distribution du tissu adipeux sur le risque de cancer, et les IMC élevés semblaient être positivement associés aux séminomes testiculaires. En ce qui concerne l'association entre l'hydrocèle et le cancer du testicule, nous n'avons malheureusement pas trouvé de résultats significatifs. En ce qui concerne les infections uro-génitales, les tumeurs non séminomateuses semblent être positivement associés à l'orchite, l'épididymite, l'orchite ourlienne et les maladies sexuellement transmissibles.

Discussion : Cette étude ne peut qu'émettre l'hypothèse d'un lien entre le cancer du testicule et les expositions intra-scrotales à la chaleur endogène (uniquement pour la hernie inguinale, l'obésité et les antécédents d'infections uro-génitales). La hernie inguinale et l'obésité étant des contre-indications à l'utilisation de la contraception thermique. Cependant, en ce qui concerne les facteurs obésité et infection génitale, ces résultats doivent être interprétés avec prudence à la lumière de l'influence d'autres pathologies et facteurs associés, et des conclusions de nouvelles méta-analyses plus récentes.

Mots clés : revue systématique, cancer testiculaire, chaleur, température.

VII. SERMENT D'HIPPOCRATE :

UNIVERSITE DE POITIERS

Faculté de Médecine et de Pharmacie

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SERMENT

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. Admis 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. Respectueux et reconnaissant 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 couvert d'opprobre et méprisé de mes confrères si j'y manque !