Technical summary report

Cannabis and cancer risk

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Report summary

- Whether or not smoking cannabis leads to cancers is still largely underdetermined.
- There is modest evidence that chronic cannabis smoking increases risk of testicular cancer and high levels of use may be a contributing factor to higher rates of testicular cancer in Māori.
- As it stands, smoked cannabis is not strongly associated with an increased risk of lung cancer and there is moderately strong evidence that cannabis use does not increase risk of cancers of the head and neck.
- Cannabis use has been implicated as a risk factor for many other cancers, but evidence is wildly conflicting, insufficient or inconclusive. Most data are from smoked combustible cannabis.
- Recreational and medicinal cannabis use is very common in NZ, particularly so for Māori and deprived groups, but declining among young New Zealanders. Based on international experience, legalisation is likely to increase regular use among people who *already* use cannabis. In overseas jurisdictions where adult cannabis use is legal, adolescent use has increased in some areas but not in others.
- Māori have one of the highest lung cancer rates in the world due to high rates of tobacco use. Although the link between cannabis use and lung cancer is uncertain, cannabis users are more likely to smoke tobacco. Cannabis regulations may impact on tobacco use by providing an alternative to tobacco **or** may promote co-use and create barriers to tobacco cessation efforts.
- Cannabis users are more likely to smoke tobacco and consume alcohol; well recognised products which cause cancers.
- From a public health perspective, it's too early to say if the overall benefits of legalising cannabis will outweigh the harms. It is important to note however, that the illegality of cannabis use has impacted on prevention efforts and there are significant criminal justice disparities under the current system.

Definitions

- The term *medicinal cannabis* refers to standardised cannabis extracts, cannabinoid-based medications and unregulated illicit 'street' cannabis that is used for self-identified medical reasons. As of December 2018, some extracts can be prescribed by a medical practitioner in NZ to treat and manage cancer-related symptoms and side effects. Palliative care patients are legally allowed to grow and use cannabis.
- The term *recreational cannabis* refers to unregulated, illicitly sourced cannabis (plant materials, synthetic, edibles, vape liquids, drinks etc.). A referendum on recreational cannabis will be held in 2020.

1. Introduction

1.1 Purpose of this report

This summary report presents a literature review of cannabis use and cancer risk and the potential role that legalising recreation cannabis may play on cancer-related inequities.

Also briefly presented in this report:

- wider public health implications of legalising cannabis
- Implications of legalising cannabis on adolescent use and co-use of cannabis with known carcinogens alcohol and tobacco.
- cannabis-related information provided by international cancer control agencies

1.2 Key background information

New Zealanders will have a chance to participate in a referendum concerning changes to cannabis legislation at the next election in September 2020. If the majority of New Zealanders vote 'Yes', the proposed *Cannabis Legalisation and Control Bill* will regulate the use, sale, cultivation and manufacture of cannabis in NZ. The intent of the Bill is to reduce harms from cannabis use to New Zealanders[1]. Surveys show that most respondents support decriminalising or legalising recreational cannabis use, although support appears to be declining [1, 2].

[1] https://www.referendums.govt.nz/cannabis/summary.html

NZ parliament recently passed a Medicinal Cannabis Bill[2] and the scheme is expected to be fully operational in 2020. It permits palliative care patients to grow and use 'illicit' cannabis; allows clinicians to prescribe approved cannabis products; and sets quality standards. Medicinal cannabis may refer to herbal unprocessed 'street' cannabis, standardised cannabis extracts and synthetic cannabinoids, some of which are medical grade [9]. Only CBD products and Sativex (for multiple sclerosis) are available on prescription, with Ministerial approval required for all other medicinal cannabis products.

The Cannabis plant contains compounds called cannabinoids, including cannabidiol (CBD) that has little to no psychoactive properties and Tetrahydrocannabinol (THC), the principal psychoactive compound. Concentrations of THC in natural cannabis preparations can vary significantly based on the plant variety, type of preparation (hash oil, smoked, vaped or ingested leaves and flowers) and cultivation technique. The CDC has confirmed that vitamin E acetate in THC vape products are primarily responsible for the recent spate of lung injuries and deaths in the US, but some uncertainty remains [3].

Excluding tobacco and alcohol, cannabis is the most commonly used drug in the world [2]. In NZ the prevalence of past year cannabis use in the general population rose significantly from 8% to 11.9% between 2011-2018. Past year use is much higher in Māori (25.5%), very deprived (15.3% vs 7% least deprived) and men (15.7% vs 8.4% in women) [4]. However, ever-use among secondary school students has declined from 39% (2001) to 23% (2012) [5]. The risk of developing dependence was 10% [6, 7]. Greater rates of dependence were reported for Māori (18-20%) [6, 8]

Around 5% of those in the NZ health Survey 2012/13 indicated they used cannabis for medical reasons over the previous 12 months (175,000 people). This represented 42% of all cannabis users surveyed. Older cannabis users reported higher rates of use [4].

New Zealanders tend to use cannabis therapeutically for depression, anxiety and chronic pain and tend not to tell their health professional(s) they are using [10]. In Australia, uptake of prescribed medicinal cannabis has been limited, with most users preferring to buy from recreational cannabis dealers [11]. The most common way NZ medicinal users consume cannabis is herbal joints (23%), bongs (23%), pipes (17%) and vapes (10%) [10]. Many are chronic users [10].

2. Methodology

- Inclusion criteria: systematic reviews and meta-analyses, new primary research not included in reviews, authoritative grey literature (e.g. WHO). A key source of

[2] http://www.legislation.govt.nz/bill/government/2017/0012/latest/DLM7518707.html

evidence was: *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research* (NASEM, 2017) [12]

- Date range: 2000-2020
- Databases searched: Medline, CINAHL, ScienceDirect, Cochrane Database of Systematic Reviews, Google Scholar

3. Findings

3.1 Is cannabis/THC carcinogenic?

- Cannabis smoke is carcinogenic in rodents and mutagenic in the Ames test
- THC is not carcinogenic in skin tests on rodents and not mutagenic in the Ames test
- Cannabis smoke shares some of the same carcinogens as tobacco smoke in higher concentrations [13] and three to four times the tar as cigarettes [14]
- Respiratory mucosa exposed to chronic cannabis smoke shows pre-cancerous molecular changes [15]

3.2 Cannabis and cancer risk

The link between cannabis use and specific cancer types is presented below. Limitations of the current evidence is well recognised - more details need to be collected on cannabis exposure assessment, frequency, duration, amount of personal use and mode of use.

Most studies examine smoked cannabis. There are only a very few rigorous studies examining health outcomes from edible or vaped cannabis (especially in direct and quantifiable comparison). However, this method of consuming cannabis is likely much safer because the carcinogenic potential of combustible cannabis is largely eliminated.

Many studies do not include heavy cannabis users and possible underreporting where cannabis is illegal are identified limitations. Furthermore, many studies do not account for possible confounders including tobacco use, human papillomavirus (HPV), and alcohol use, although has this has improved in more recent research.

3.2.1 Lung cancers

- A 2018 metanalysis of observational studies found an overall significant increased risk of lung cancer and cannabis (marginally significant OR = 1.76, 95% CI 1.00-3.08; I^2 = 82.0%)[20].
- A systematic review of 12 observational studies in 2016 reported that 8 included studies indicated an increased risk of lung cancer from cannabis use or lung cancer occurrence (4 reported no association or lower risk)[18]. One of the included studies, found long term cannabis use increases the risk of lung cancer in young NZ adults. For each year of cannabis smoking (one joint/day/year), the risk of lung cancer was estimated to increase by 8% (after adjusting for confounders including tobacco smoking) [19].
- A pooled analysis of case-control studies (2015) found little evidence for an increased risk of lung cancer in habitual or long-term cannabis smokers and no evidence of a dose−response relationship [17]. Heavy consumption was not examined.
- A 2006 systematic review found no association between cannabis smoking and lung cancer [16].

Conclusion: at present, smoked cannabis is not strongly associated with an increased risk of lung cancer, despite cannabis smoke containing known carcinogens

3.2.2 Head and neck cancers

- Studies reported increased and decreased risks, either because there is no association or because risks differ by HPV status, geographical status or other factors.
- A metanalysis in 2015 of case-control studies did not find an overall association for head and neck cancers (HNCC) [21], which conflicted with the findings of an earlier pooled analysis conducted in 2013. This reported an elevated risk of oropharyngeal and a reduced risk of tongue cancer in ever cannabis smokers compared with never cannabis smokers [22].
- The INHANCE Consortium reported three large population based case-control studies and found no link between cannabis and squamous cell HNCCs (controlled for alcohol and tobacco), whereas a case–control study with over 400 HNCCs subjects recently found (after adjusting for confounders) that 10–20 years of cannabis use was associated with a significantly *reduced* risk of HNSCC (OR 0.38, 95% CI 0.22–0.67)

- There is some evidence that smoked cannabis may raise the risk of HPV associated HNSCC [22]

Conclusion: smoked cannabis is not strongly associated with an increased risk of head and neck cancers

3.2.3 Testicular cancers

- The majority of well-designed case control studies report an increased risk of testicular cancer with cannabis use.
- A metanalyses found an odds ratio of 1.5 for high frequency cannabis users and an odds ratio of 1.5 for those who had used cannabis for 10 or more years.
- A 2017 Swedish study of 49,343 men followed up for 42 years found no significant relation between lifetime ever cannabis use and development of testicular cancer (AHR 1.42, 95% CI, 0.83, 2.45) [24].
- A 2015 metanalyses of data primarily collected in the 1990s observed that current, chronic and frequent cannabis use was associated with the development of testicular cancer [23]. The strongest association was found for non-seminoma development (those using cannabis on at least a weekly basis had 2.5 times greater odds of developing a non-seminoma testicular cancer compared those who never used cannabis (OR: 2.59, 95 % CI 1.60–4.19). Inconclusive evidence for cannabis use and the development of seminoma tumours.

Conclusion: cannabis use is associated with the development of testicular cancer

3.2.4 Child cancers

- A few case-control studies have reported parental cannabis smoking during pregnancy was associated with increased risks of cancers among children (leukaemia [25, 26], astrocytoma [27], and rhabdomyosarcoma [28]) but dose response relations were not assessed, there were small numbers of exposed cases, and these studies have not been replicated [29].
- Another two case control studies found no association between parental cannabis use and childhood neuroblastoma [30] and childhood acute myeloid leukaemia [31].

Conclusion: inconsistent findings. No firm conclusions can be drawn

3.2.5 Other cancers (brain, colorectal, melanoma, breast, bladder, prostate, cervical)

- Often smaller sized and fewer studies, many unmeasured confounders and varying methods in quantifying cannabis use. Cause and effect relationship has not been established.
- A Large study of 65,000 participants found no increased risk of **head and neck, lung, colorectal, melanoma, or breast** cancer in experimenters, former or current users (controlled for tobacco use, alcohol intake and SES).
- An elevated risk (3-fold) for **prostate** cancer and **cervical** cancer (1.4 fold risk) has been reported (but no statistically significant risk found when participants compared with non-cannabis smokers and controlled for potential confounders)
- A US study of 105,005 participants found an increased risk of malignant primary **gliomas** (RR 2.8, 95% CI 1.3–6.2) in people who smoked cannabis once per month or more
- A recent cohort study of 84,170 participants reported an inverse relationship between cannabis use and **bladder** cancer [32]

3.3 Cancer risk for people who self-medicate with cannabis

- The potential harms described above may apply to people who use illicit cannabis for medical reasons, and recreational users, particularly if they are heavy, regular users

of combustible cannabis. Most self-medicated users in NZ also use cannabis recreationally [33]

- Self-medicated cannabis use is widespread among patients with cancer in the US, Canada, Australia and UK, and legalisation significantly increased the likelihood of use. The high cost of legal medicinal cannabis is barrier to access in Australia [34-36].
- New Zealanders who use cannabis for self-prescribed medical reasons often do so for several years, usually for anxiety, depression and pain [10]
- Many medicinal users prefer to smoke cannabis over oral cannabinoid medication [10, 37]. Edibles and vaping are also reported to be popular [38].
- There is a lack of consistency in formulation and labelling of cannabis products in international jurisdictions where recreational and medicinal cannabis industries are regulated.

3.4 Cannabis-related cancer inequities

- Given the higher cannabis use among Māori and deprived groups and the disparity in cannabis dependence between Māori and non- Māori, cannabis may be a contributing factor to ethnic and socioeconomic disparities in testicular cancer.
- Māori men are 80% more likely to develop testicular cancer than non-Māori men (RR 1.80, 95% CI 1.58-2.05) [23] and are more likely to die from testicular cancer. By comparison, NZ Pacific Island men and men of European ethnicity have a very low rates [39].
- NZ men with low incomes had a higher risk of testicular cancer than those with high incomes/low deprivation [39]
- Legalisation is likely to increase regular use among people who use cannabis [40] and potentially further increase cancer disparities.
- 137 (34 Māori) cases of testicular cancer were diagnosed in NZ in 2013 and 6 men died.
- Māori women have one of the highest rates of lung cancer in the world and around 5000 New Zealanders die of diseases caused by (legal) tobacco smoking every year. Thousands more live with a smoking-related disability. Cannabis regulations may impact on tobacco use by providing an alternative to tobacco or may promote co-use and create barriers to tobacco cessation efforts [41].

- Nicotine vapes are currently promoted as a tobacco cessation tool by the Government and are viewed as potential inequity ‘disrupters’. It should be noted that by vaping rather than smoking combustible cannabis will largely eliminate the carcinogenic potential of smoked cannabis. However, cannabis concentrates mixed with dangerous oil/solvents are also vaped, and a particular solvent – vitamin E acetate – is causing deaths and lung illnesses in the United States. THC vape products are easily accessible in NZ. If gains are to be made in disrupting tobacco inequities through the promotion of nicotine-containing vapes, regulations and safety standards will need to be responsive to all vaped substances.
- Significantly more Māori used alcohol, a class 1 carcinogen, with cannabis than the general population [4, 42]
- Cannabis use may contribute to cancer disparities, but this should be weighed with current inequities in criminal justice penalties. Māori are more likely to be arrested and convicted for minor drug offences [43] and Māori struggling with substance abuse are less likely to be able to access treatment [44].
- A joint statement issued by Hāpai Te Hauora Maori Public Health states that regulating cannabis should be about achieving equity and justice, i.e. regulations should be “designed with and by Māori, under a Te Tiriti o Waitangi framework, and that they work to promote the mana motuhake of hapū and iwi Māori” https://www.drugfoundation.org.nz/assets/uploads/2019-uploads/Kaupapa-Maori-statement-FINAL-with-signatures.pdf

Containers of marijuana on display at a dispensary in San Francisco. Source: www.statnews.com

3.5 Implications of legalising cannabis on adolescent use (and co-use with alcohol and tobacco)

- Of consideration is whether legalising medical or recreational use increases adolescent cannabis use (and potential harms). This is difficult to determine - so far adolescent recreational use has increased in some international jurisdictions that have liberalised cannabis [34-37], but not in others [36, 38-42].
- Liberal medicinal cannabis laws overseas have facilitated the legalisation of supply for recreational use [17] – a pathway NZ may follow.
- Smoke-free restrictions have been widely adopted in NZ resulting in historic low adolescent tobacco smoking levels (3% 15-17-year olds), whereas restrictions on cannabis use have been relaxing.
- There is a high but declining lifetime prevalence of cannabis use among 15-24-year olds (21% in 2012, down from 38% in 2001)[5]. Declines were also seen among young Maori and those from low decile schools [45].
- There may be a link between using cannabis and tobacco and alcohol use, both Class 1 carcinogens [46, 47]. In countries with high adolescent cannabis use and low tobacco use (such as NZ), cannabis use in non-smokers may predict a 'reverse gateway' to later tobacco use [48]. The causal relationship is not established but the association raises concern. It is likely that several factors are at play including adolescent risk taking, peer influence, ease of accessibility, price and general willingness to engage in drug taking.
- Fergusson and Boden [49] state that among young New Zealanders, cannabis use is widespread but "harmful effects are largely confined to a minority of heavy and regular users" (p242). This point emphasises the need for a risk reduction approach if cannabis is legalised (see 3.7), together with significant investment in treatment support for dependant users.

3.6 Public health implications of cannabis legalisation

- Legalising cannabis may *increase* the known risks of cannabis use: vehicle fatalities, mental health harms, lung illnesses and neurocognitive impairments. Legalisation may *reduce* use and associated harms from opioids, tobacco, alcohol and other drugs [27]. Legislation is at such an early stage, so long public health effects are

uncertain. Cannabis legislative reform is outpacing regulatory efforts to minimise potential public health harms.

- The Prime Minister has asked the Chief Scientist to provide an evidence report on the broader impacts of cannabis. The report is due to be released before the referendum in September 2020 and will be available here: https://www.pmcsa.ac.nz/our-projects/cannabis/
- In a recent Lancet series, Hall and colleagues [40] argue that the extent to which use and harm might increase will depend on whether the legal market is taxed and regulated "in ways that will increase or decrease harms caused by cannabis, alcohol, opioids and other drugs…" (p1587)

3.7 International cancer control agencies and cannabis information

No position statement on cannabis use and cancer was found although three agencies produced online information on this issue for the public. The agencies all focused on the efficacy of medical use, even in countries that have legalised recreational use.

Agency	Position statement		Online consumer information*	
	Cancer risk – non medical use	Therapeutic use	Cancer risk – non medical use	Therapeutic use
American Cancer Society				marijuana-and-cancer
National Cancer Institute				cannabis-pdq
Cancer Research UK			cannabis and cancer-the-evidence-so-far	cancer/treatment/complementary-alternative-therapies/cannabis cannabis and cancer-the-evidence-so-far
Australian Cancer Council		Position statement - Medical use of cannabis.pdf		cannabis-for-medical-purposes
Cancer Australia				
Canadian Cancer Society			cannabis-and-cancer risk	medical-cannabis-and-cannabinoids
Canadian Partnership Against Cancer			lower-risk-guidelines-cannabis-pdf cannabis-and-cancer	cannabis-and-cancer
WHO			Effects non-medical use	

3.8 Lower risk guidelines for consumers

Evidence-based guidelines for lower risk cannabis use are designed to inform users and improve public health outcomes in settings with permissive cannabis legislation. One example is presented below.

Some points are relevant to cancer prevention, such as: ‘smoking cannabis is the most harmful way of using cannabis’. The guidelines may also be adapted to include more cancer prevention content, including ‘don’t use tobacco and cannabis together’.

Lower-Risk Cannabis Use Guidelines (for non-medical users) [50]:

- Remember that every form of cannabis use poses risks to your health. The only way to completely avoid these risks is by choosing not to use cannabis. If you decide to use cannabis, follow these recommendations to lower risks to your health.
- The earlier in life you begin using cannabis, the higher your risk of serious health problems. You’ll lower your risk of cannabis-related health problems if you choose to start using cannabis later in life
- Higher-strength or more powerful cannabis products are worse for your health. If you use, choose low-strength products, such as those with a lower THC content or a higher ratio of CBD to THC.
- Don’t use synthetic cannabis products. Using these can lead to severe health problems, such as seizures, irregular heartbeat, hallucinations and in rare cases, death.
- Smoking cannabis (for example, smoking a joint) is the most harmful way of using cannabis because it directly affects your lungs.
- If you choose to smoke cannabis, avoid inhaling deeply or holding your breath. These practices increase the amount of toxins absorbed by your lungs and the rest of your body and can lead to lung problems.
- The more frequently you use cannabis, the more likely you are to develop health problems, especially if you use on a daily or near-daily basis.
- Cannabis use impairs your ability to drive a car or operate other machinery. Don’t engage in these activities after using cannabis, or while you still feel affected by cannabis in any way.

- Some people are more likely to develop problems from cannabis use. Specifically, people with a personal or family history of psychosis or substance use problems, and pregnant women should not use cannabis at all.
- Avoid combining any of the risky behaviours described above. The more risks you take, the greater the chances of harming your health as a result of cannabis use.

Full version can be accessed here: Canadian Research Initiative in Substance Misuse: http://crismontario.ca/Pages/LRCUG.UserBrochure.Revision.English.Final.pdf

4. Conclusions

Current evidence indicates that people who smoke cannabis appear to have a higher risk of testicular cancer. But overall, it remains unclear whether cannabis use can increase cancer risk. In part, this is due to the fact that undertaking this research and measuring cannabis consumption accurately is very challenging.

Along with methodological challenges, research on the health effects of cannabis has been limited due to its illegality and this has hindered evidence-based policymaking. It is likely that better data will become available as more jurisdictions legalise cannabis.

It is also not known if cannabis plays a large role in cancer inequities, nor do we know whether the broader public health benefits will outweigh the risks. The proposed *Cannabis Legalisation and Control Bill* creates an authority that will commission research on these issues, and this can inform future actions taken by the Cancer Society. The link between cannabis use and tobacco and alcohol is a particular area to monitor carefully, along with the potential for cannabis use in non-smokers to lead to later tobacco use.

The Cancer Society can play a role in informing the public of the uncertainties around cannabis and cancer risk and advice on proven therapeutic uses for people with cancer and cancer survivors.

Cannabis store in Los Angeles. Source: Laurie Avocado https://flic.kr/p/4dqEiT (CC BY 2.0)

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