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The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

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Cancer

Chapter Highlights
• The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head and neck) in adults.
• There is modest evidence that cannabis use is associated with one sub-type of testicular cancer.
• There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

Cancer is a major public health problem in the United States. With 1,685,210 new cancer cases and 595,690 cancer-related deaths expected to occur in 2016, it is a leading cause of disease and death among Americans (NCI, 2016). Cannabis use has been associated with cigarette smoking—to which 28.6 percent of all cancer deaths in the United States in 2014 have been attributed—and, like tobacco smoke, cannabis smoke contains carcinogens (Lortet-Tieulent et al., 2016; Tashkin, 2013). These potential risk factors for cancer have prompted epidemiological research examining the association between cannabis use and the risk of developing several types of cancer, including lung, head and neck, testicular, esophageal, and other cancers that occur in adults, as well as cancers that occur in children. The present chapter reviews the findings of three recent, good- to fair-quality systematic reviews, including one pooled analysis, as well as three primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in six formal conclusions.

CANCER

Is There an Association Between Cannabis Use and the Incidence of Lung Cancer?

Systematic Reviews

Zhang et al. (2015) pooled data on 2,159 lung cancer cases and 2,985 controls from six case-control studies, four of which were unpublished. The impact of key characteristics of cannabis smoking (e.g., intensity and duration of cannabis smoking, cumulative exposure, age at start of smoking) on lung cancer incidence was evaluated for all study participants and for a sub-group who were not tobacco smokers. Among all study participants, there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (odds ratio [OR] 0.96, 95% confidence interval [CI] = 0.66–1.38);

similarly, among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR 1.03, 95% CI = 0.51–2.08).[1] When only adenocarcinoma cases were compared to controls, Zhang et al. (2015, p.898) observed a "suggestive," but still statistically non-significant, association between lung cancer incidence and either smoking more than 1 joint/day (OR 1.73, 95% CI = 0.75–4.00) or having a cumulative exposure of more than 10 joint-years (OR 1.74, 95% CI = 0.85–3.56).

Primary Literature

Huang et al. (2015) conducted an epidemiologic review on the association between cannabis use and the incidence of several cancers, including lung cancer. They evaluated six studies on lung cancer, including Zhang et al. (2015) and two studies included in that review. Of the three remaining studies, two were described by Zhang et al. (2015) as having several limitations, including an inability to adequately control for tobacco use and potential reporting bias, and are not discussed here. The third study evaluated lung cancer risk among 49,321 Swedish male military conscripts over a 40-year period and found that, compared with participants who had reported never using cannabis, those who reported using cannabis more than 50 times at baseline had a statistically significant risk of developing lung cancer (hazard ration [HR] 2.12, 95% CI = 1.08–4.14) after adjusting for tobacco and alcohol use and other confounders (Callaghan et al., 2013).[2]

Discussion of Findings

Zhang et al. (2015) found no statistically significant association between smoking cannabis and lung cancer incidence; this was true for all study participants as well as for the sub-group of study participants who were not tobacco smokers. Although the risk of lung cancer increased as the duration and intensity of cannabis use increased, even participants who smoked most often and for the longest periods of time were not at significantly greater risk than non-habitual smokers. Huang et al. (2015) did not perform a meta-analysis of the lung cancer studies; studies included in that review but not in Zhang et al. (2015) indicate an increased risk for lung cancer associated with smoking cannabis.

Both studies noted several limitations. Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking, the study did not adjust or account for tobacco

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[1] Non-habitual cannabis smokers were defined as those with cumulative cannabis consumption of less than 1 joint-year, including never users. Subjects who did not smoke tobacco were those who reported smoking less than 100 cigarettes over their lifetime, or who fit the cut-offs used in the pooled studies.

[2] There were 49,321 participants at the start of the study, and 44,257 participants involved in the assessment of cannabis risk. Hazard ratio (HR) includes adjustments for tobacco smoking, alcohol consumption, respiratory conditions, and socioeconomic status at time of conscription.

or cannabis during the 40-year follow-up period, the authors were unaware whether study participants mixed tobacco and cannabis, and the self-reporting process was not anonymized.

> **CONCLUSION 5-1** There is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.

Is There an Association Between Cannabis Use and the Incidence of Head and Neck Cancers?

Systematic Reviews

De Carvalho et al. (2015) conducted a systematic review and meta-analysis of nine case-control studies derived from 6 articles and totaling 13,931 study participants (5,732 cases and 8,199 controls) in order to evaluate the association between cannabis use and the incidence of head and neck cancers, including upper aerodigestive tract, oral cavity, and nasopharyngeal cancers as well as on head and neck squamous cell carcinoma. After adjusting for tobacco use, age, gender, and race, the meta-analysis found no significant association between cannabis use and head and neck cancers (OR 1.021, 95% CI = 0.912–1.143). The authors concluded that there was "insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of [head and neck cancers]" (de Carvalho et al., 2015, p. 1755).

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head and neck cancers and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

In their review, de Carvalho et al. (2015) noted several limitations particular to individual studies. First, although a non-significant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers.

> **CONCLUSION 5-2** There is moderate evidence of no statistical association between cannabis use and the incidence of head and neck cancers.

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Is There an Association Between Cannabis Use and the Incidence of Testicular Cancer?

Systematic Reviews

Gurney et al. (2015) conducted a systematic review and meta-analysis on the association between cannabis use and testicular germ cell tumors. The authors identified three case-control studies totaling 2,138 study participants (719 cases and 1,419 controls). Compared to participants who never smoked cannabis, participants who reported ever smoking cannabis had a statistically non-significant increased risk of developing testicular germ cell tumors (OR 1.19, 95% CI = 0.72–1.95). By comparison, statistically significant associations between cannabis use and the risk of developing testicular germ cell tumors were seen for the subgroups of participants who were current smokers (OR 1.62, 95% CI = 1.13–2.31) or who reported smoking cannabis at least once a week (OR 1.92, 95% CI = 1.35–2.72) or for 10 years or longer (OR 1.50, 95% CI = 1.08–2.09). Among current users, including the subgroups of those who used cannabis at least once weekly or for at least 10 years, the risk of developing non-seminoma tumors was higher than the risk of developing seminoma tumors. For example, compared to never smokers, participants who smoked at least once per week had a statistically significant risk of developing non-seminoma tumors (OR 2.59, 95% CI = 1.60–4.19), while the risk for developing seminoma tumors was not statistically significant (OR 1.27, 95% CI = 0.77–2.11). Gurney et al. (2015) observed that, because non-seminoma tumors are frequently diagnosed at a younger age than seminoma tumors, the stronger association between cannabis use and non-seminoma tumors suggests "puberty (rather than later in life) as the key point of exposure" (Gurney et al., 2015, p. 8).

Primary Literature

Huang et al. (2015) conducted a review and meta-analysis of the same three studies reviewed by Gurney et al. (2015) and found no association between participants who had ever smoked cannabis and the risk of developing testicular cancer. However, compared to participants who had never smoked cannabis, heavy users who had smoked one or more times per day or week (OR 1.56, 95% CI = 1.09–2.23) and chronic users who had smoked for 10 years or longer (OR 1.50, 95% CI = 1.08–2.09) had a statistically significant risk of developing testicular cancer.

Discussion of Findings

Gurney et al. (2015) found a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. By comparison, cannabis use was not associated with a statistically significant risk of developing seminoma-type testicular germ cell tumors. Lacking further evidence, an extrapolation of this association to other types of testicular cancer is unwarranted. Huang et al. (2015) found an association between the incidence of testicular cancer (without further specification) and cannabis use that was frequent or of long duration.

Gurney et al. (2015) highlighted several limitations of their review. First, each of the three case-control studies informing the review relied on self-report without biological validation, and the two studies that utilized interviews to collect this data did not indicate whether the interviewers were blinded to the case-control status of the participants. Self-report data cannot be verified and unblended interviewers are a potential source of bias. Second, two of

the studies reported responses rates that were both low and unequal: 67.5 percent to 38.2 percent response rate for cases and 73.3 percent to 43.3 percent response rate for controls. Differences in the prevalence of cannabis use among participants who did and did not respond could bias the odds ratios calculated in these studies. Third, the high and growing prevalence of cannabis use in the general population may render the category "ever-smoker" uninformative, since it will encompass not only frequent and chronic users but also individuals who have only minimal exposure to the drug. A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders: three studies controlled for age and a history of cryptorchidism, two controlled for alcohol and drug use, and only one controlled for other substance use.

As noted in Gurney et al. (2015), Huang et al. (2015) did not distinguish between seminoma and non-seminoma-type tumors and also failed to assess the quality of the reviewed studies. Additionally, the review included limited information on the methods used to conduct the meta-analysis.

> **CONCLUSION 5-3** There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumors.

Is There an Association Between Cannabis Use and the Incidence of Esophageal Cancers?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and esophageal cancer.

Primary Literature

The committee identified one primary research study that addressed a potential association with esophageal cancer. To assess the association between cannabis use and the incidence of lung and upper aerodigestive tract cancers, Hashibe et al. (2006) conducted a large population-based case-control study involving 1,040 controls and 1,212 cases, 108 of which were diagnosed with esophageal cancer. Investigators collected data on the use of cannabis, tobacco, and alcohol as well as relevant medical, environmental, and socioeconomic information. After adjustments were made for demographic factors and alcohol and tobacco use, study participants with cumulative cannabis exposure equal to 1 to 10 joint-years were found to have a statistically non-significant decreased risk of developing esophageal cancer compared to participants who never used cannabis (OR 0.77, 95% CI = 0.36–1.6). The risk was further depressed, but still not statistically significant, for participants whose cumulative cannabis exposure was equal to 30 or more joint-years (OR 0.53, 95% CI = 0.22–1.3). Among participants who never smoked cigarettes, the risk of esophageal cancer was not statistically different between those who had ever smoked cannabis and those who had never smoked cannabis (OR 0.79, 95% CI = 0.30–2.1).

Discussion of Findings

In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants. On account of these efforts to preemptively address methodological issues, few limitations were identified that could account for the lower risk of esophageal cancer among cannabis smokers as compared to non-smokers—an unexpected, though not statistically significant, result. The participation rate among esophageal cases was low at 35 percent, creating a potential source of bias if the prevalence of cannabis use was much higher or lower among non-participants with esophageal cancer than among participants with esophageal cancer. The subgroup of participants with esophageal cancer and high levels of cumulative cannabis exposure (i.e., ≥30 joint-years) was relatively small (n = 9), thereby limiting the ability to detect an association between cannabis use and cancer incidence in this group. As with other studies, confounders may not have been entirely controlled for, and measurement errors may have persisted. The authors note these potential limitations, but also speculate that "it is possible that such inverse associations may reflect a protective effect of marijuana" (Hashibe et al., 2006, p. 1833).

> **CONCLUSION 5-4** There is insufficient evidence to support or refute a statistical association between cannabis smoking and the incidence of esophageal cancer.

Is There an Association Between Cannabis Use and the Incidence of Other Cancers in Adults?

Systematic Reviews

The committee identified no systematic reviews on the association between cannabis exposures and the incidence of other cancers.

Primary Literature

In an epidemiologic review, Huang et al. (2015) reported on the association between cannabis use and the risk of several types of cancer. A cohort study involving 27,920 men and 36,935 women age 15–49 years found that, compared to participants who did not smoke cannabis, self-reported current or former use of cannabis on more than 6 occasions was associated with prostrate cancer in men that never smoked cigarettes (relative risk [RR] 3.1, 95% CI = 1.0–9.5) and with cervical cancer in women that never smoked cigarettes (RR 1.6, 95% CI = 1.2–2.2), after adjusting for age, race, education, and alcohol use (Sidney et al., 1997). However, when compared to participants who did not smoke cannabis or who had smoked cannabis on only 1–6 occasions, those who were current or former cannabis smokers were not at statistically significant risk of developing prostate or cervical cancer, after adjusting for tobacco and alcohol use and other potential confounders.

Another large cohort study involving 133,881 participants aged 25 years and older found that, compared to non-use of cannabis, self-reported cannabis use at least once a month was associated with a statistically significant risk of malignant adult-onset glioma compared to non-

use of cannabis, after controlling for potential confounders, including demographic and socioeconomic factors and alcohol and tobacco use (RR 2.8, 95% CI = 1.3–6.2) (Efird et al., 2004). Compared to participants who did not use cannabis, there was statistically signficant risk of developing brain tumor among those participants who reported using cannabis weekly (RR 3.2, 95% CI = 1.1–9.2) or monthly (RR 3.6, 95% CI = 1.3–10.2).

Huang et al. (2015) also reviewed two studies on non-Hodgkin lymphoma risk. Holly et al. (1999) conducted a population-based case-control study involving 3,376 women and heterosexual men to determine risk factors for non-Hodgkin lymphoma. Compared to participants who never used cannabis, those who reported using cannabis less than 40 times had a statistically significant decreased risk of developing non-Hodgkin lymphoma, after adjusting for age, sex, and education (OR 0.68, 95% CI = 0.55–0.84). Among participants who used cannabis on 40 or more occasions, the risk of non-Hodgkin lymphoma was further depressed (OR 0.57, 95% CI = 0.44–0.74). In another population-based case-control study, 378 HIV-negative men and women diagnosed with non-Hodgkin lymphoma were matched by age, biological sex, race, language of interview, and neighborhood of residence at time of diagnosis to HIV-negative controls (Nelson et al., 1997). There was no statistically significant difference in the risk of developing non-Hodgkin lymphoma among participants who reported using cannabis at any time, as compared to those who reported never using cannabis (OR 0.86, 95% CI = 0.50–1.48). The lack of a statistical difference in non-Hodgkin lymphoma risk between cannabis users and non-users was true whether participants reported using cannabis only 1–5 times (OR 0.68, 95% CI = 0.34–1.38) or on more than 900 occasions (OR 1.09, 95% CI = 0.48–2.48).

Other studies reviewed by Huang et al. (2015) examined the association between cannabis use and the risk of Kaposi's sarcoma, and penile and anal cancer. Maden et al. (1993) conducted a case-control study involving 110 cases and 355 age matched controls to identify risk factors for penile cancer. After adjusting for alcohol and cigarette use, age, and number of sexual partners, there was no statistically significant difference in the risk of developing penile cancer among participants who reported ever using cannabis as compared to those who never used cannabis (OR 1.5, 95 % CI = 0.7–3.2). In a case-control study on risk factors for anal cancer, 148 men and women diagnosed with anal cancer were matched by age, biological sex, year of diagnosis, and area of residence to 166 male and female controls diagnosed with colon cancer (Daling et al., 1987). There was no statistically significant difference in the risk of anal cancer among participants who had ever used cannabis, as compared to those who had never used cannabis, after adjsuting for age, residence, and cigarette use (RR 0.8, 95% CI = 0.2–4.0). Chao et al. (2009) conducted a cohort study to determine the association between use of cannabis and other recreational drugs and the risk of Kaposi's sarcoma in homosexual men coinfected with HIV and human herpes virus 8 (HHV-8). Among 1,335 participants, those who used cannabis in the 6 months preceding data collection were not significantly more likely to develop Kaposi's sarcoma than participants who did not use cannabis during that period (HR 1.00, 95% CI = 0.79–1.28), after adjusting for potential confounders including alcohol use, tobacco smoking, and characteristics of sexual activity.

To assess the association between cannabis use and bladder cancer risk, Thomas et al. (2015) reviewed data from 84,170 men aged 45-69 years old who were participants in the California Men's Health Study. After adjusting for age, race, and body mass index, the risk of developing bladder cancer was significantly reduced for participants who used cannabis but not tobacco, compared to those who used neither cannabis nor tobacco (HR 0.55, 95% CI = 0.31–1.00). After stratifying cannabis use by levels of cumulative cannabis exposure, the authors

found that the depression in bladder cancer risk was statistically significant only for participants who reporting smoking cannabis on 3–10 occasions (HR 0.57, 95% CI = 0.34–0.96). Similarly, stratification by participant age revealed that, among participants who smoked cannabis but not tobacco, the risk of bladder cancer was significantly decreased only for those were age 45–54 years (HR 0.26, 95% CI = 0.07–0.92). In a case-control study involving 52 Veterans Affairs patients younger than 61 years old and age-matched to 104 controls, Chacko et al. (2006) found that a significantly higher proportion of cases as compared to controls reported ever using cannabis (88.5 percent versus 69.2 percent, p = 0.008). The mean number of joint-years of cannabis smoked was also signficantly higher among cases than controls (48.0 joint-years versus 28.5 joint-years, p = 0.022). After adjusting for potential confounders, including tobacco use, a statistically significant association between increasing joint-years of cannabis and the risk of transitional cell carcinoma remained (p trend = 0.01).

Discussion of Findings

Huang et al. (2015, p.26) reviewed eight studies that reported on the association between cannabis use and prostate, cervical, anal, bladder, and penile cancer, as well as glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma, and concluded that "there are still insufficient data to make any conclusions on an association with marijuana". Separately, Thomas et al. (2015) found no statistically significant difference in the risk of developing bladder cancer among participants who used cannabis but not tobacco as compared to those who used neither. These studies have several limitations.

In the study on cervical and prostate cancers, Sidney et al. (1997, p.727) relied on self-report to determine patterns of cannabis use and did not assess for changes in those patterns during follow-up. The study cohort included no participants older than 49 years old age at baseline, and participants were followed for a mean of 8.6 years; consequently, the study was unable to ascertain whether there is an association between cannabis use and the incidence of cancer in older populations. The authors stated that they "do not consider any of the findings to be conclusive".

In the study on malignant adult-onset glioma, investigators did not assess for changes in patterns of cannabis use after baseline, only a small number of cases (n = 8) reported using cannabis at least once a month, and more than 1 in 4 cases (26 percent) did not provide data on cannabis use (Efird et al., 2004). Holly et al. (1999) note that responses to questions concerning events that occurred many years previously (e.g., lifetime cannabis use) or addressing sensitive topics (e.g., illegal drug use) can be affected by recall and response biases, respectively. Nelson et al. (1997) also list recall bias as a potential limitation. Of these two studies, Huang et al. (2015) note that the association between cannabis use and risk of non-Hodgkin lymphoma may be the result of confounding cause by the observed protective association of sexual behavior and cocaine use. For a discussion on the effectiveness of cannabis and cannabinoids as a treatment for glioma and other cancers, see chapter 4.

Maden et al. (1993) assert that the low rate of participation among cases (50.2 percent) and controls (70.3 percent) was a major limitation of their study on penile cancer. In the study on anal cancer, Daling et al. (1987) note that all control participants were diagnosed with colon cancer. Other investigators have noted that this control group may not be appropriate for assessing the association between cannabis use and anal cancer incidence, as cannabis smoking is a potential risk factors for colorectal cancer (Hashibe et al., 2005). Limitations of the study on

Kaposi's sarcoma include the lack of consistent HHV-8 testing for all participants, the use of non-continuous categories for describing frequency of cannabis use and the resultant potential for ambiguous reporting, and the use of self-report to collect data on patterns of cannabis use (Chao et al., 2009).

Thomas et al. (2015) note that the observational design of their study creates the potential for participation and response biases. Other limitations of the study include the failure to differentiate the risks for bladder cancer associated with current as opposed to former cannabis use, the lack of an evaluation of other potential risk factors for bladder cancer, and the fact that the study findings apply only to men. Findings from Chacko et al. (2006) are limited by a high proportion of ever tobacco smokers among both cases (94.2 percent) and controls (93.3 percent). According to Huang et al. (2015), the limitations of this study also include its small size, the use of self-report to collect data on cannabis use, and failing to adjust for tobacco smoking–an acknowledged bladder cancer risk factor.

Further research is needed to better characterize whether and how cannabis use is associated with the risk of developing these cancers. Additionally, since important biological distinctions exist among cancers that occur in a given organ, including histological and molecular sub-types, such research will need to separately investigate and identify the risk factors associated with each.

CONCLUSION 5-5 There is insufficient evidence to support or refute a statistical association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.

Is There an Association Between Parental Cannabis Use and the Incidence of Cancer in Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between parental cannabis use and subsequent cancer incidence in offspring.

Primary Literature

Huang et al. (2015) reviewed 3 studies on the association between parental cannabis use and the risk of leukemia. Robison et al. (1989) conducted a case-control study involving 204 cases diagnosed with acute non-lymphoblastic leukemia (ANLL) by 17 years of age that were matched to controls by age, race, and residential location. Maternal use of cannabis during, and in the year preceding, pregnancy was associated with a statistically significant risk of ANLL (RR 10, $p = 0.005$). By comparison, the risk of ANLL associated with paternal use of cannabis during the same period was not statistically significant (RR 1.47, $p = 0.32$). Children whose mothers used cannabis during, or in the year preceding, pregnancy, were significantly younger in the age at diagnosis of ANLL than children whose mothers did not use cannabis during this period (37.7 months [mean] versus 96.1 months [mean], $p = 0.007$). There was also a statistically significant difference in the distribution of morphological types of ANLL cases between cases and controls ($p = 0.02$). For example, M1/M2 and M4/M5 morphologic types respectively comprised 10 percent and 70 percent of ANLL cases among children whose mothers used cannabis, while they

comprised respectively 58 percent and 31 percent of cases among children whose mothers did not use cannabis. Logistic regression to identify independent risk factors for ANLL found that "maternal marijuana use was the single most predictive factor" identified in the study (Robison et al., 1989, p. 1907).

In contrast to these findings, Trivers et al. (2006) conducted a case-control study involving 517 case diagnosed with acute myeloid leukemia (AML) by 17 years of age and matched to 610 controls by age, race, and residential location, and found that children whose mothers used cannabis during, or in the 3 months preceding, pregnancy were at significantly lower risk of developing AML than children whose mothers did not use cannabis during that period, after adjusting for household income and parental age and education (OR 0.43, 95% CI = 0.23–0.80).[3] Among children whose mothers reported using cannabis in the 3 months before pregnancy, those whose mothers used cannabis at least once weekly had a lower risk of developing AML than those whose mothers used cannabis less than once weekly (OR 0.19, 95% CI = 0.06–0.59 versus OR 0.57, 95% CI = 0.26–1.29). Although overall paternal use of cannabis was significantly associated with the risk of AML (OR 1.37, 95% CI = 1.02–1.83), there was no statistically significant association between paternal use of cannabis during, and in the three months preceding, pregnancy and the risk of AML (OR 1.02, 95% CI = 0.67–1.53). The authors concluded that "[p]arental marijuana use is unlikely as a strong risk factor for childhood AML" (Trivers et al., 2006, p. 117).

Finally, Wen et al. (2000) conducted a case-control study to evaluate the association between exposures related to paternal military service, such as cannabis use, and the incidence of AML or acute lymphoblastic leukemia (ALL) in their children. Among 2,343 cases diagnosed with AML or ALL and matched by age, race, biological sex, and residential location to 2,723 controls, participants whose fathers had ever used cannabis had a statistically significant risk of developing ALL or AML compared to those whose fathers had never used cannabis (OR 1.5, p< 0.01).

Huang et al. (2015) also reviewed studies on the association between parental cannabis use and the incidence of rhabdomyosarcoma, neuroblastoma, and astrocytoma in pediatric populations. A case-control study of 322 children younger than 21 years of age and diagnosed with rhabdomysarcoma matched by age, race, and biological sex to 322 controls found that children whose mothers used cannabis in the 12 months before their child's birth were significantly more likely to develop the disease than children whose mothers had not used cannabis during this period (OR 3.0, 95% CI = 1.4–6.5), after adjusting for complications during pregnancy and other potential confounders (Grufferman et al., 1993). Similarly, children whose fathers used cannabis in the year prior to their child's birth were at significantly greater risk of developing rhabdomyosarcoma than children whose fathers did not use cannabis at this time (OR 2.0, 95% CI = 1.3–3.3). However, use of cannabis and cocaine were highly correlated, as was maternal and paternal use of cannabis, making it impossible to isolate the effects of maternal and paternal cannabis use from each other or from the effects of parental cocaine use.

Kuijten et al. (1990) conducted a case-control study involving 163 cases diagnosed by 14 years of age with astrocytoma or related tumors and matched to controls by age, race, and residential location, and found a borderline statistically significant association between maternal use of cannabis in the 10 months preceding their child's birth and the risk of astrocytoma (OR

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[3] Acute myeloid leukemia and acute non-lymphoblastic leukemia refer to the same type of cancer.

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2.8, 95% CI = 0.9–9.9, p = 0.07).[4] By comparison, maternal use in the 9 months preceding their child's birth was not associated with the risk of astrocytoma (OR 4.0, p = 0.11).

Bluhm et al. (2006) examined the association between maternal cannabis use and the risk of neuroblastoma in their offspring. Among 538 cases diagnosed with neuroblastoma by 19 years of age age-matched to 504 controls, maternal use of cannabis during pregnancy, as compared to non-use of cannabis during any measured time period, was significantly associated with greater risk of neuroblastoma in their offspring, after adjusting for use of other recreational drugs (OR 2.51, 95% CI = 1.18–5.83). After stratifying maternal use of cannabis by time period, the authors found a statistically significant association between the incidence of neuroblastoma and maternal use of cannabis during the first trimester (OR 4.75, 95% CI = 1.55–16.48), but not between neuroblastoma incidence and maternal cannabis use in the second or third trimester, in the month preceding conception, or in the period between birth and diagnosis. Age at diagnosis, but not frequency of maternal cannabis use, had large effects on neuroblastoma risk. For example, among children diagnosed with neuroblastoma before 12 months of age, maternal cannabis use was significantly associated with risk of neuroblastoma (OR 15.61, 95% CI = 3.07–285.89), while the risk was similar for children whose mothers used either less than one or more than one pipeful of cannabis during the first trimester (OR 4.16, 95% CI = 1.52–14.61 and OR 4.42, 95% CI = 1.09–29.58).

Discussion of Findings

Findings on the association between parental cannabis use and risk of pediatric leukemia were mixed: maternal cannabis use in the months preceding birth was determined to be at once a risk factor for, and protective against, the development of ANLL/AML in children (Robison et al., 1989; Trivers et al., 2006). Differences in the design of questionnaires employed in these studies, including the extent to which questions on recreational drug use were distinguished from other exposure questions, may have affected participant reporting and contributed to these contradictory results. Limitations of Robison et al. (1989) include findings based on small sample sizes (9 cases), wide confidence intervals for risk estimates, and the possibility that, as a consequence of the large number of parameters analyzed in the study, the association between ANLL incidence and maternal cannabis use was a chance finding. Although the reported frequency of maternal cannabis use was considerably lower in Robison et al. (1989) than in other studies, there was no evidence of difference in reporting between cases and controls. In Trivers et al. (2006), reported rates of maternal cannabis use were lower among cases and higher among controls than in other studies, suggesting the potential for differences in reporting by cases and controls.

While Robison et al. (1989) and Trivers et al. (2006) found that paternal cannabis use during and in the months preceding pregnancy was not associated with ANLL/AML incidence in their offspring, Wen et al. (2000) found that any paternal cannabis use was significantly associated with the incidence of AML or ALL in their offspring. Limitations in Wen et al. (2000) included the potential for selection bias due to a lower participation rate among controls than cases, and potential for residual confounding due to the lack of data on the duration and frequency of exposure to cigarette smoking. A similar lack of data on patterns of cannabis use

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[4] Cases were diagnosed with astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements, or brainstem glioma.

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(e.g., duration, frequency, cumulative exposure) prevented investigation of a dose-response relationship between paternal cannabis use and risk of ALL in their offspring.

Grufferman et al. (1993) found that parental cannabis use was significantly associated with the incidence of rhabdomyosarcoma in their offspring, and Bluhm et al. (2006) found that maternal cannabis use during the first trimester was significantly associated with neuroblastoma. In the latter study, very few mothers reported using cannabis more than once per day during any of the measured time periods, suggesting the potential for underreporting the frequency of cannabis use. Additionally, there was insufficient data to assess dose-response relationships, findings on paternal cannabis use were limited due to low response rates, and confidence intervals were wide due to the small number of women reporting cannabis use during and just before pregnancy. In Grufferman et al. (1993), 25 percent of cannabis users were also cocaine users. As a result of this correlation, any association between parental cannabis use and risk of rhabdomyosarcoma is confounded by polysubstance use. In addition, the authors did not collect data on frequency and duration of cannabis use, and were therefore unable to assess for a dose-response relationship.

> **CONCLUSION 5-6** There is insufficient evidence to support or refute a statistical association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.

RESEARCH GAPS

To address the research gaps relevant to cancer incidence, the committee suggests the following:

- There is need for robust epidemiological studies to investigate the association between cannabis exposure and several types of cancers, including but not limited to lung, head and neck, testicular, and esophageal cancers.
- Further investigation is needed to resolve any contradictory findings on, and to characterize the nature and strength of, any potential associations between parental cannabis use and the risk of cancer in their offspring.
- To promote the development of a body of high-quality evidence on the association between cannabis exposure and cancer incidence, researchers need to prioritize rigorous study designs and implement data collection protocols and methods that allow them to control for key confounders and to precisely measure cannabis exposure.
- Because of changing exposures to cannabis and the fact that many associations are based on single studies, replication of existing studies in targeted areas is needed.

SUMMARY

The committee identified good or fair quality systematic reviews on the association between cannabis use and the risk of lung, testicular, and head and neck cancers. Good quality primary literature on the association between cannabis use and lung, testicular, esophageal,

childhood, and several other cancers was also identified. Due to a paucity of research, mixed findings, and numerous methodological limitations, the committee judged the evidence from the studies on childhood cancers, esophageal cancer, and various other cancers in adults to be insufficient to support or refute a statistically significant association between cannabis use and the incidence of these cancers. More conclusive findings and less extensive methodological limitations in the literature on lung, testicular, and head and neck cancers allowed the committee to conclude that there is moderate evidence that there is no statistically significant association between cannabis use and the incidence of lung or head and neck cancer, and limited evidence that there is a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cells tumors. Below, Box 5-1 summarizes the chapter conclusions.

Epidemiological studies that investigate the association between cannabis use and the risk of various cancers risk face methodological challenges similar to those found in studies of other clinical outcomes. These challenges include but are not limited to small sample sizes and low participation rates, the inability to verify cannabis use data based on self-report alone, and difficulties in controlling for potential confounders and accounting for potential effect modifiers. Additionally, some special—if not unique—methodological challenges pertain to cancer studies. For example, cancer is a diverse set of diseases that occur in different organs and organ systems, and have different histopathological characteristics and risk factors. Some of these risk factors, such as family cancer history, occupational exposures, and diet, are difficult to measure and were often not accounted for by the studies review in this chapter. Additionally, the long incubation period of many cancers requires a similarly extended observation period, and makes it difficult to fully characterize the relevant cannabis exposure and to control for other relevant exposures.

Future research will need to address the limited scope and quality of epidemiological studies on the association between cannabis use and cancer incidence. Investigators will need to confirm existing evidence on lung and head and neck cancers, and to expand the evidence base on testicular, esophageal, and childhood cancers, as well as other cancers in adults. To address the methodological limitations described above, future studies will also need to be well-designed and to employ rigorous methods of data collection and measurement.

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BOX 5-1
Summary of Chapter Conclusions*

There is moderate evidence of *no* statistical association between cannabis use and:
- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:
- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:
- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

*Numbers in parentheses correspond to chapter conclusion numbers.

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