Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Statements of Principles Nos. 53 and 54 of 2014
in respect of Malignant Neoplasm of the Prostate

Request for Review Declaration No. 30

1. In relation to the Repatriation Medical Authority (RMA) Statements of Principles **No.53** malignant neoplasm of the prostate made under subsections 196B of the Veterans' Entitlements Act 1986 (the VEA), the Specialist Medical Review Council (the Council) under subsection 196W(5) of the VEA:

   DECLARES that there is **insufficient** sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include factor/s for smoking cigarettes, or the equivalent thereof in other tobacco products and the **clinical onset** of malignant neoplasm of the prostate.

2. In relation to the RMA Statement of Principles **No. 54** concerning malignant neoplasm of the prostate, made under subsection 196B of the VEA, the Council :

   DECLARES under subsection 196W(5) of the VEA, that there is **insufficient** sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include factor(s) for smoking cigarettes, or the equivalent thereof in other tobacco products and the **clinical onset** of malignant neoplasm of the prostate; and

   DECLARES , under subsection 196W(4)(c) that there is **sufficient** sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include factor(s) for smoking cigarettes, or the equivalent thereof in other tobacco products and the **clinical worsening** of malignant neoplasm of the prostate; and

REMITS and DIRECTS under subsection 196W(4)(d) the RMA to characterise a factor concerning smoking cigarettes, or the equivalent thereof in other tobacco products and the **clinical worsening** of malignant neoplasm of the prostate, taking into account whatever new information has become available since the SoPs were determined in 2014, and having particular regard to determining evidence-based thresholds for pack-years smoked, and where smoking has ceased, for years since smoking cessation.

INDEX of CONTENTS

REASONS FOR DECISIONS

INTRODUCTION

1. The Specialist Medical Review Council (the Council) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application the Council is to review as relevant:

   - the contents of Statement/s of Principles in respect of a particular kind of injury, disease or death; or
   - a decision of the RMA not to determine, not to amend, Statement/s of Principles in respect of a particular kind of injury, disease or death.

2. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information which was actually used by the RMA as opposed to information which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is at Table 2 of Appendix D.

3. Fundamental to Statements of Principles, and so to a Council review, is the concept of sound medical-scientific evidence (SMSE), as that term is defined in section 5AB(2) of the VEA[i].

4. The SMSE relevant to this application (the relevant SMSE) is listed in Table 1 of Appendix D.

5. The information to which the Applicant and the Council referred, being information which the RMA advised was new information, that is, information which was not available to the RMA at the relevant times, and so was not

---

[i] The SMSE is a subset of the available information. It comprises those articles which the Council considers:

a) are relevant to the matters within the proposed scope of review, and

b) satisfy the definition in the VEA of 'sound medical-scientific evidence'.

Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

"Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

a) the information:

(i) is consistent with material relating to medical-science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or

(ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

b) in the case of information about how that kind of injury, disease or death may be caused – meets the applicable criteria for assessing causation currently applied in the field of epidemiology.

The later requirement is held to mean 'appropriate to be taken into account by epidemiologists'.

considered by the Council in reaching its review decision is listed as "new information" in Table 1 of Appendix D.

6. Appendix C sets out further details regarding the composition of the Council for this review and the legislation relating to the making of Statements of Principles.

SCOPE OF THIS REVIEW

7. In their application, the Applicant sought review of the contents of Statements of Principles **Nos 53 and 54 of 2014 for Malignant Neoplasm of the Prostate.** The Applicant contended that there was SMSE on which the RMA could have relied to amend either or both Statements of Principles in respect to **smoking and clinical onset of Malignant Neoplasm of the Prostate.**

8. The Council, when reviewing the SMSE, must determine whether there is SMSE which indicates a reasonable hypothesis connecting the particular injury, disease or death to the relevant service.

9. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant service. In a reasonable hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'[ii]

10. If the Council is of the opinion that a reasonable hypothesis has been raised, the Council proceeds also to determine whether a connection exists to relevant service on the balance of probabilities,[iii] i.e. whether the connection is more probable than not.

11. In these Reasons, the associations for both the reasonable hypothesis test and the balance of probabilities test are respectively referred to as the 'relevant association'.

12. The Council exercises its scientific judgement in weighing the evidence about the relevant association.

Council's decision on the scope of review

13. The Council wrote to both the Applicant and the Commissions advising its decision on its proposal to limit the scope of the review to:

[ii] See the full Federal Court decision in *Repatriation Commission v Bey* (1997) 79 FCR 364 which cited with approval these comments from Veterans' Review Board in *Stacey* (unreported 26 June 1985), all of which were in turn cited with approval in the Moore J decision at [33].

[iii] Relevant service in balance of probabilities statements of principles refers to non-operational service having regard to the various definitions applying to types of 'service' as defined in the VEA and the MRCA.

- the possible inclusion of a factor or factors, as contended, for smoking cigarettes, or the equivalent thereof in other tobacco products and the clinical onset of malignant neoplasm of the prostate.

14. In their submission to the SMRC, the Commissions supported the retention of a factor relating to smoking and worsening of malignant neoplasm of the prostate in instrument 53 of 2014. Further, it submitted that it would be reasonable for the Council to direct the RMA to include a factor for current or recent smoking and worsening of malignant neoplasm of the prostate in instrument 54 of 2014.

Council's decision on the revised scope of review

15. The Council subsequently wrote to both the Applicant and the Commissions advising its decision to expand the proposed scope of the review and invited comment. No comments were received on the proposed scope of the review and therefore the Council decided that without limiting the scope of the Council's review of (some or the whole of) the contents of the Statements of Principles (SoPs), it will have particular regard, to whether there was sound medical-scientific evidence upon which the RMA could have relied to amend either or both of the SoPs in the following way:

a) the possible inclusion of a factor or factors, as contended, for smoking cigarettes, or the equivalent thereof in other tobacco products and the clinical onset of malignant neoplasm of the prostate; and

b) the possible inclusion of a factor or factors, as contended, for smoking cigarettes, or the equivalent thereof in other tobacco products and the clinical worsening of malignant neoplasm of the prostate.

Written and oral submissions

16. The Council took into account the submissions made to it, both written and in oral form.

Applicant

17. In summary, the Applicant represented by Mr James Wain, National president of the Vietnam Veterans, Peacekeepers and Peacemakers Association, and Mr Ross Dunn, confined their concerns to the written submission made to the Council by the Commissions.

18. They submitted that Huncharek et al[1] provides evidence that supports the link between tobacco consumption and prostate cancer and that this, together with other papers, provides a reasonable hypothesis of a connection between smoking and prostate cancer.

19. The Applicant's representatives considered that the Commissions had identified papers selectively and they queried why, for example, the study by McLaughlin et al[2] had not been included in the pool of available information. They submitted that McLaughlin[2] had reported an increased risk for prostate cancer mortality among both former and current smokers, as well as a clear dose response effect.

20. The Applicant also questioned why the Commissions had not included the most recent US Surgeon-General's report (2014)[3], which they submitted states, "…that the evidence is suggestive of a higher risk of death from prostate cancer in smokers than non-smokers and that, in many who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less well differentiated cancer in smokers than in non-smokers".

21. The Applicant submitted that the criteria used by the Commissions for identifying studies was not transparent or explicit and there was no evidence that the Commissions had used validated tools, such as the Newcastle-Ottawa Scale, for assessing the quality of papers.

22. The Applicant also raised concerns about the narrative approach employed by the Commissions, and submitted that a meta-analysis would have been less open to criticisms of selection bias.

23. The Applicant submitted that statistically insignificant results had been included in the pool of data and that this had "…diluted the overall effect".

Commissions

24. The Commissions made a written submission to the Council on 18 May 2015 and a Medical Officer representing the Commissions made an oral submission complementing the Commissions' written submission at the Council's meeting on 31 July 2015.

25. In summary, the Commissions submitted that the best quality evidence available to the RMA on the role of smoking in the causation of prostate cancer comes from prospective cohort studies of prostate cancer incidence.

26. The Commissions noted that the meta-analysis by Huncharek et al[1] only considered studies that were published between January 2006 and February 2007. Two large studies by Watters et al[4], and Rohrmann et al[5], were not included, and the Commissions contended that Huncharek's "…main analysis of incident prostate cancer risk in current smokers based on data that is largely unadjusted for potentially important cofounders such as diet and weight; and, includes other analyses that appear to be inaccurate …".

27. The Commissions contended that the best available data on risk of incident prostate cancer (overall) from smoking comes from Watters et al[4] who they submitted, had comprehensively controlled for potential confounders.

28. The Commissions contended that another large study by Rohrmann et al[5] and other prospective cohort incidence studies identified, as well as nested case-control studies, showed either no effect or a weak protective effect for smoking on prostate cancer risk.

29. The Commissions submitted that, "…for incident prostate cancer there are several studies that do report a positive association with smoking, but there are more studies, of considerably better quality and power, that indicate the reverse, along with a group of further studies that support no association.".

30. The Commissions commented on three such studies: "Adami et al (1996)[6], "…which found a weak positive association in current smokers, but which did not adjust for potential confounders; Hiatt et al (1994)[7], which reported an elevated risk in current smokers of one or more packets per day (not adjusted for dietary fat intake); and Cerhan et al (1997)[8], a much smaller study, which had positive findings, particularly for advanced disease, but which also had limited adjustment for confounders.".

31. The Commissions submitted that Giovannucci et al[9] had the most sound methodology and controlled for a range of potential confounders, including dietary fat. It also updated smoking status every two years during follow-up and was able to use detailed and accurate smoking data to undertake a range of analyses relating to the timing of tobacco use. The study found smoking to be unrelated to prostate cancer incidence.

32. The Commissions concluded that, "…when analysed collectively the evidence reviewed in this submission indicates quite strongly that there is no overall causal association between smoking and the development of prostate cancer."

33. The Commissions contended that, "…in contrast to the incidence data, the studies looking at prostate cancer mortality do show a fairly consistent association with current smoking."

34. The Commissions submitted that Zu and Giovannucci[10] reviewed the evidence for smoking and aggressive prostate cancer "… (and) concluded that smoking is likely to be a risk factor for prostate cancer progression."

35. The Commissions supported the reinstatement of the worsening factors from the Balance of Probabilities SoPs, Number 54 of 2015.

Council's decisions on the relevant SMSE

36. The Council considered that the SMSE to be assessed in the review should comprise information:

- that was available to the RMA at the relevant times;
- which was sent by the RMA to the Council under section 196K of the VEA;

37. which was considered by the Council to be sound medical-scientific evidence as defined in section 5AB(2). The Council's final decision on the SMSE for the review was that it should comprise the information listed at Table 1 of Appendix D.

38. Information which the RMA advised was not available to it at the relevant times was not taken into account by the Council for the purposes of the review, as it could only be considered as 'new information'.

PREVIOUS COUNCILS' REVIEWS OF STATEMENTS OF PRINCIPLES IN RESPECT OF MALIGNANT NEOPLASM OF THE PROSTATE

39. The Council has previously considered the contended smoking factor in earlier reviews of now revoked Statements of Principles in respect of malignant neoplasm of the prostate. The Convener selected a newly constituted Council to conduct this review to avoid any potential issues with respect to the apprehension of bias or prejudgement arising from involvement in an earlier review.

40. On 22 December 1995, a previously constituted Council published its Declaration and Reasons for Decision in respect of now revoked Statements of Principles 95 and 96 of 1995. On 2 August 2001, another previously constituted Council published its Declaration and Reasons for Decision in respect of Instruments Numbered 191 and 192 of 1996. On 16 August 2012, another previously constituted Council published its Declaration and Reasons for Decision in respect of Instruments Numbered 28 and 29 of 2005. Copies of the three previous declarations and Reasons for Decision are available on the Council's website.

COUNCIL'S EVALUATION OF THE SMSE

41. When evaluating the SMSE, the Council focussed on the information relevant to the scope of the review and listed at Table 1 of Appendix D.

42. In forming its decisions on the SMSE, the Council brings to bear its scientific expertise and judgement. The Bradford Hill criteria and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the articles, as it considered appropriate.

43. The Council also considered any methodological limitations or flaws (including such things as statistical power, control of confounders, bias, exposure assessment methods etc.) in the various articles.

44. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:

- strength of association
- consistency across investigation
- specificity of the association
- temporal relationship of the association
- biological gradient
- biological plausibility
- coherence
- experiment
- analogy

45. The Council notes that these criteria are not necessary conditions of a cause and effect relationship. They act to provide some circumstantial evidence of such a relationship.

46. While the Council considered, it did not focus its evaluation on those articles that:

- were reviews of available information that the Council has evaluated in these reasons for decisions;
- did not provide data that the Council could draw conclusions from about smoking and malignant neoplasm of the prostate.

COUNCIL'S CONCLUSIONS ON THE RELEVANT SMSE FOR CLINICAL ONSET

47. In reaching a decision about the existence or otherwise of a reasonable hypothesis the Council must consider and evaluate all of the SMSE. In the situation where there is a single piece of evidence, such as a single study or paper, in support of a reasonable hypothesis, on its own that may be enough to support the hypothesis. However, this information should be considered with other SMSE in identifying whether the SMSE indicates the relation to the medical condition. It is therefore important that the Council considered all information in context.

48. From the information that was available to the RMA at the relevant time, the Council considered all studies relevant to the scope of this review. In considering the matters within the scope of the review, the Council closely analysed those studies, both individually and collectively, taking into consideration both quantitative and qualitative evidence in its evaluations.

49. In its considerations of **clinical onset of malignant neoplasm of the prostate**, the Council concentrated on studies confined to incidence only, as "incidence" is the best way to determine if an exposure "causes" disease. Mortality inevitably

includes the effects of variables that influence outcome of disease once diagnosed, of which prior or continuing smoking might be one such variable.

50. Meta-analyses were used to quantitatively and systematically assess the available information and derive conclusions from the more precise estimates generated on the effect of smoking on prostate cancer incidence, than any individual study contributing to the pooled analysis. Meta-analysis is a well establish method to synthesise research result.

51. The Council's view was that a meta-analysis approach was most appropriate in this case to consolidate and quantitatively review the vast, complex, and conflicting studies that have reported on smoking and prostate cancer incidence. The Council also noted that the Applicant for this review supported meta-analyses as the most suitable approach.

52. The meta-analyses conducted for this review focussed on studies that the RMA advised were available to it when it last determined the SoPs for malignant neoplasm of the prostate. Separate meta-analyses were also conducted using studies from a new paper by Islami et al[11].

53. Sensitivity analyses were also performed to evaluate the impact of potential biases. For the methods and results of the meta-analyses performed, refer to Appendix A.

54. The Council reviewed the results of the meta-analyses of the information that was available to the RMA and determined that the evidence does not support an association between smoking (current or former) and increased incidence of prostate cancer.

55. Neither unadjusted analyses, nor analyses that were adjusted for potential confounding factors such as age, diet, body mass index, etc. identified a relationship between smoking and increased prostate cancer risk.

56. The Council reviewed the results of the meta-analyses stratified by studies conducted before and after the introduction of the Prostate Specific Antigen (PSA) test, and found the evidence does not support an association between smoking (current) and increased incidence of prostate cancer before or after the introduction of the PSA test.

57. The introduction of the PSA test may have increased the number of indolent cancers identified (i.e. cancers where treatment may not be necessary as they are unlikely to progress). It has been proposed that smoking may have a positive association with non-indolent cancers, and that the increased identification of indolent cancers in recent years could be one explanation for a greater number of studies identifying an association between smoking and prostate cancer incidence,

having been published prior to the introduction of PSA screening (i.e. studies with follow-up data collected prior to 1990), but not after.

58. It has also been suggested that non-smokers are more likely than smokers to utilise screening, and that the introduction of PSA screening has increased the number of diagnoses in non-smokers which may attenuate a positive association between smoking and prostate cancer incidence.

Comments on studies relied on by the Applicant

59. In weighing up and considering the outcomes of the meta-analyses the Council is cognisant of the legislative task before it which is to identify whether there is information amounting to SMSE upon which it might rely. Accordingly, the Council has given specific consideration to the papers relied on by the applicant and their impact in light of the meta-analyses of all of the information before the Council.

60. The applicant relied on a meta-analyses performed by Huncharek[1]. In their Meta-analysis, Huncharek et al[1] reviewed 16 studies in relation to smoking and prostate cancer incidence. The authors reported that current smokers had no increased risk of incident prostate cancer (RR = 1.04; 95% CI = 0.87, 1.24). However in sub-analyses that included four cohort studies Cerhan et al[8], Lotufo et al[12], Nilsen et al[13], Rohrmann et al[14] current 'heaviest' smokers, categorised by (>15 to >20 cigarettes per day), were reported to be at increased risk of incident prostate cancer (RR = 1.22; 95% CI = 1.01, 1.46).

61. No association was found in any of the analyses included in the Council's meta-analyses of the information available to the RMA regarding smoking dosage (cigarettes per day) and incident prostate cancer risk.

62. Huncharek et al[1 (p. 694)] also reported that "incident cancer risk among current smokers measured in years or pack years of smoking (highest versus lowest) from five cohort studies containing such information (Adami (1996)[6], Cerhan (1997)[8], Giovannuchi (2007)[9], Lotufo (2000)[12] and Nilsen (2000)[13] were also consistent with a small but significant increase in prostate cancer risk (RR = 1.11; 95% CI = 1.01, 1.22)."

63. These five studies were available to the RMA. In the Council's meta-analyses regarding smoking dosage (pack years) and prostate cancer incidence, only one of these studies, Cerhan,[8] was included as it was the only study of the five that reported adjusted data.

~~64.~~ The findings from the Council's meta-analysis were that no associations between smoking dosage (pack-years) and increased prostate cancer risk were identified in the twelve studies reviewed.

65. Many of the additional studies available to the RMA, and included in the Council's meta-analysis, were available to Huncharek et al,[1] i.e. Cerhan et al[8], Lotufo et al[12], Putnam et al[15], Plakson et al[16], Le Marchand et al[17], Nilsen et al[13], and are cited in their paper, but were not included in their sub-analyses for reasons that the Council assumes were due to their pre-determined criteria for inclusion of studies based on a statistical test for homogeneity. Despite using this criterion, the analyses by Huncharek[1] still included studies in their sub-analyses where the exposure variable for dosage was measured differently (for example Giovannucci et al[9] reported smoking data in years and not pack years) and the data was unadjusted for potential confounding factors.

66. Fifteen of the studies considered by Huncharek et al[1] in relation to smoking and prostate cancer incidence were available to the RMA. The one study not available to the RMA was by Allen et al[18]. The Allen et al[18] study consisted of a sample of atomic-bomb survivors recruited from Nagasaki and Hiroshima, Japan. It reported that smoking was not associated with prostate cancer risk (RR = 0.80; 95% CI = 0.60, 1.07). A different study by Kondo et al[19] of atomic-bomb survivors recruited from Nagasaki, Japan, was available to the RMA and reported more comprehensive smoking dosage data than Allen et al[18]. Kondo et al[19] concluded that, "…the RR for current smokers compared with never smokers was 0.70 (95% CI, 0.58–0.86), which was in agreement with previous results."[19 (p.1370)]

67. The applicant also relied on "The Health Consequences of Smoking – 50 Years of Progress" produced by the US Surgeon-General[3]. The US Surgeon-General reported on the health consequences of smoking and concluded that, "The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer."[3 (p8)]. This conclusion is consistent with the conclusions reached by the Council.

68. The Council concluded that the evidence supports a conclusion that smoking is not a risk factor for the onset of prostate cancer.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR SMOKING CIGARETTES, OR THE EQUIVALENT THEREOF IN OTHER TOBACCO PRODUCTS AND THE CLINICAL ONSET OF MALIGNANT NEOPLASM OF THE PROSTATE.

69. The Council concluded that its review of the SMSE did not point to the relevant association for clinical onset. As, in the Council's view, the reasonable hypothesis test was not met, the balance of probabilities test necessarily could not be met.

COUNCIL'S ANALYSIS OF THE NEW INFORMATION

70. As mentioned above, in conducting a review, the Council is unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times. However, having formed the view that there was nothing in the pool of information which pointed to the relevant association, and being mindful

of the Applicant's comments, the Council considered whether in its view there was a basis for recommending to the RMA that it (the RMA) undertake a new investigation.

71. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, by reason of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new information (listed at Table 1 of Appendix D) which it considered on a preliminary basis.

72. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any directions or recommendations to the RMA.

73. In the Council's view any such direction or recommendation should only be made by the Council if it formed the view that the new information comprised sound medical-scientific evidence as defined in section 5AB(2).

COUNCIL'S ANALYSIS OF THE NEW INFORMATION FOR CLINICAL ONSET

74. The Council noted a new meta-analysis by Islami et al[11]. This paper, which was published after the SoPs were last reviewed by the RMA, was based on an extensive search of the literature on the association between smoking and prostate cancer incidence and death.

75. Islami et al[11] included 22 studies in their meta-analyses and found that cigarette smoking at baseline was inversely associated with prostate cancer incidence (RR: 0.90; 95% CI = 0.85-0.95), i.e. it was associated with reduced prostate cancer risk.

76. Islami et al[11] conducted additional analyses that considered the number of cigarettes smoked, cumulative dosage, and confounding variables and did not find an association between smoking and increased prostate cancer risk. The studies included by Islami et al[11] in their meta-analysis of information on smoking and prostate cancer incidence were included in additional meta-analyses by the Council. Inclusion of these additional studies did not change the conclusions reached from the meta-analyses conducted on the information that was available to the RMA.

77. The Council considered that the new paper by Islami et al[11] supports its conclusions about the information that was available to the RMA.

COUNCIL'S CONCLUSIONS ON THE RELEVANT SMSE FOR CLINICAL WORSENING

78. The Council considered "worsening" to be plausible, given the well-established associations between smoking and many causes of mortality. For this reason, and

due to the smaller number of relevant studies, the Council restricted itself to a narrative consideration of the available studies.

79. To evaluate clinical worsening, four associations were considered, including studies on the risk of smoking and prostate cancer death in men after diagnosis with prostate cancer; prostate cancer mortality; prostate cancer recurrence; and studies on disease stage.

80. Of the three papers that considered the risk of smoking and prostate cancer death in men after diagnosis with prostate cancer, one study, Kenfield et al[20], found a statistically significant positive association, (RR=1.61, 95%CI: 1.11-2.32). The other two studies[28, 29] found RRs that were >1.0 but not statistically significantly so. For details, see Table 1 of Appendix B.

81. Of the 21 studies with data on the association between cigarette smoking ("current" smokers compared with "never" smokers) and prostate cancer mortality risk, nine studies, [32, 6, 33, 34, 35, 9, 24,20, 32] found a positive, statistically significant association (RR range = 1.18 95% CI = 1.09-1.28 to 1.8 (1.1-2.9); and all other studies, except two, found an RR that was >1.0 but not statistically significantly. See Table 2 of Appendix B for details.

82. Of the eight studies that considered current cigarette smoking of 20 or more cigarettes per day and prostate cancer mortality, all found a positive association (RR>1), three of which were statistically significant. For example, Rohrmann e al[5], found that, "...a high intensity of smoking (RR= 1.81, 95% CI: 1.11-2.93, 25 + cigarettes per day vs non-smokers) and a long duration of smoking (RR= 1.38, 95% CI: 1.01-1.87, 40 + years vs non-smokers) were associated with a statistically significantly increased risk of prostate cancer death."[5 (page 710)]

83. Only one study, Kenfield et al, [20] considered pack-years smoked and prostate cancer mortality, and observed that smokers of more than 40 pack-years had a significantly increased risk of prostate cancer mortality, (RR= 1.82, 95%CI: 1.03-3.20).

84. Of the five studies with data on the association between cigarette smoking, smoking ("current" smokers with "never" smokers) and prostate cancer recurrence, all found a positive association (RR>1) and three [22, 20, 21] were statistically significant. Pickles et al [21], found an increased risk of recurrence in current smokers treated with curative external beam radiation therapy (RR=1.68, 95%CI: 1.11-2.56). Joshu et al[22] found an increased risk of prostate cancer recurrence one year after prostatectomy, (RR= 2.31, 95%CI: 1.05-5.10). Kenfield et al[20], found an increased risk of recurrence in current smokers (RR 1.61, 95%CI: 1.16-2.22). See Table 3 of Appendix B.

85. Of the 10 studies with data on the association between cigarette smoking, smoking ("current" smokers with "never" smokers) and disease stage, three studies found a statistically significant positive association between current cigarette smoking and higher stage cancers. In the US health professionals study, Kenfield et al[21], found an increased risk in men with clinical stage T2 (RR= 1.33, 95%CI: 1.17-1.51), and stage T3 and T4 (RR= 2.82, 95%CI: 1.85-4.31). In patients treated with curative external beam radiation therapy, Pickles et al[21], found a statistically increased risk in men with clinical T3, (RR= 1.37, 95%CI: 1.12-1.68), and T4 (RR= 3.64, 95%CI: 1.18-11.17). Kobrinsky et al[23] found a statistically increased risk for metastatic cancer (RR= 1.53, 95%CI: 1.17-2.02) and regional cancer (RR= 1.83, 95%CI: 1.09-3.06). The results of the other nine studies were broadly consistent with such an association although not statistically significant. See Table 4 of Appendix B.

86. All studies considered (except Weinmann et al[24]) were prospective cohort study designs of overall good quality. Many adjusted for significant known confounders. Weinmann et al[24] found a statistically significant association between current smokers and prostate cancer mortality (RR 1.5 95% CI = 1.1-2.0).

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR SMOKING CIGARETTES, OR THE EQUIVALENT THEREOF IN OTHER TOBACCO PRODUCTS AND THE CLINICAL WORSENING OF MALIGNANT NEOPLASM OF THE PROSTATE.

87. The council found that there was SMSE that pointed to an association between current smoking and the risk of prostate cancer progression and death, particularly for current and heavy smoking.

88. The Council was satisfied that the SMSE that was available to the RMA supports the current factor in the reasonable hypothesis Statement of Principles No. 53 for clinical worsening.

89. The Council went on to consider whether there was SMSE to support an association on the balance of probabilities. It found that there is evidence strong enough to support a judgement of a probable causal relationship. A consistent association has been observed in the available studies between exposure to current smoking and the risk of prostate cancer progression and death, but it could not confidently rule out chance, bias or confounding.

90. The Council observed that a dose response gradient was reported in a number of the available studies. However, the available studies did not report on pack-years smoked, making it difficult to determine a suitable threshold for cumulative smoking exposure that is suitable for use in the SoPs. The Council considered that it may be possible to determine a threshold for baseline smoking exposure and mortality using a meta-regression method similar to that undertaken by Islami et al 2014[11].

91. Accordingly, the Council recommended that the RMA conduct a new investigation to find out whether the available and new information provides evidence for a threshold for cumulative smoking exposure and the clinical worsening of prostate cancer.

92. The Council considers that there is good evidence that current smoking causes clinical worsening based on the studies reviewed in the attached Tables 1 and 2. However, the Council was less certain about former smoking (including time since cessation). The Council acknowledges there may be additional studies that should be considered but that were not available to the RMA at the relevant times.

93. Therefore, the Council directs the RMA to consider revision to the SOPs for current smoking and clinical worsening, with particular attention to the amount smoked. The RMA should also investigate characterising factors for former smokers and clinical worsening, with particular attention to amount smoked and elapsed time since the cessation of smoking.

94. In making this direction, the Council was not pre-judging the outcome of what such an investigation may elicit.

COUNCIL'S ANALYSIS OF THE NEW INFORMATION ON CLINICAL WORSENING

95. Islami et al[11], performed a meta-analysis on 19 articles on smoking and risk of death from prostate cancer and reported that smoking at baseline was associated with an increased risk of death from prostate cancer, (RR: 1.24; 95% CI, 1.18–1.31). Isamli et el [11] found the results were consistent across the studies and that there was little evidence of publication bias. The results did not change substantially when studies that did not adjust for confounders were excluded.

96. Islami et al[11] also reported a dose response (cigarettes per day) associated with death from prostate cancer based on 12 studies, (p=0.02; RR for 20 cigarettes per day = 1.20). Islami et al[11] did not discuss the concept of pack-year-history, and although accepting a relationship between smoking and death from prostate cancer, did not consider the temporal component of duration of smoking habit.

97. The Council's view is that the new paper by Islami et al[11], supports its conclusions about an association between current smoking and the risk of prostate cancer progression and decreased survival.

98. The Applicant relied on a cohort study of U.S. Veterans on smoking and cancer mortality by McLaughlin[2]. This cohort study found a non-significant positive association between smoking and prostate cancer mortality. The data was unadjusted for potential confounding factors.

99. Since the publication of Islami et al 2014[11], more reviews and studies have been published including, Ordonez-Mena et al, 2016[25] and Rieken M et al 2015[27]. The conclusions reached by these studies support the finding of a relationship between smoking and clinical worsening.

DECISION

100. The Council made the declarations summarised in paragraphs 1 and 2 above.