Analysis of Concordance

Supplemental Material II: Statistical Measures of Concordance between Animal and Human Tumours

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in collaboration with and endorsed by other participants (see the Contributors list)
in the Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis,
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Krewski et al. (2018) conducted a comprehensive analysis of the concordance between tumours seen in animals and humans for 111 distinct Group-1 agents identified in the IARC Monographs programme through Volume 109, based on information abstracted from the IARC Monographs by Grosse et al. (2018). Concordance analysis was based on the 60 agents with sufficient evidence of carcinogenicity both in humans and in animals, with at least one tumour site specified for humans and at least one tumour site specified for animals. For simplicity of presentation, analysis of concordance was based on the overlap between tumour sites expressed in animals and humans (Krewski et al., 2018, Table 7, Figure 9).

Concordance between animal and human tumour sites is based on the overlap between animal and human tumour sites, as shown in Supplemental Table 6 (all animals) and Supplemental Table 7 (mice and rats). Let N_h, N_a, and N_b denote the number of agents demonstrating a particular tumour site in humans, animals, or both humans and animals, respectively. The total number of agents demonstrating tumours at this site is then $N_t = N_h + N_a - N_b$. Concordance is measured by the percentage overlap, calculated as $(N_b/N_t) \times 100\%$. These results are shown in the column headed 'overlap' in Supplemental Tables 6 and 7. [The 'overlap' results in Supplemental Table 6 are the basis of the evaluation of concordance in Table 7 of Krewski et al. (2018)]

The WG was also interested in the overlap between agents demonstrating tumours in animals at a particular site with agents demonstrating tumours in humans at that site, calculated as $(N_b/N_h) \times 100\%$. These results are shown in the column headed 'animal/human overlap' in Supplemental Tables 6 and 7, and reflect the percentage of agents demonstrating tumours at the site of interest in humans that have also been seen to cause tumours at that site in animals. [The 'animal/human overlap' results in Supplemental Table 6 are the basis of the analysis of overlap between animal and human tumours in Panel A of Figure 9 in Krewski et al. (2018)]

Conversely, the 'human/animal overlap' column in Supplementary Tables 6 and 7, calculated as $(N_b/N_a) \times 100\%$, reflects the percentage of agents demonstrating tumours at the site of interest in animals that have also been seen to cause tumours at that site in humans. [The 'human/animal overlap' results in Supplemental Table 6 are the basis of the analysis of overlap between human and animal tumours in Panel B of Figure 9 in Krewski et al. (2018)]

More formal statistical analyses of concordance may be based on a comparison of animal and human tumours summarized in the form of the following 2x2 table.

Animals	Humans		
	Positive	Negative	Total
Positive	N_{11}	N_{12}	$N_{1.}$
Negative	N_{21}	N_{22}	$N_{2.}$
Total	$N_{.1}$	$N_{.1}$	N_t

Here, N_{11} denotes the number of agents for which the tumour site of interest was observed in both animals and humans, N_{22} denotes the number of agents for which the tumour site was seen in neither animals nor humans, N_{21} denotes the number of agents positive in humans and negative in animals, and N_{12} denotes the number of agents positive in animals and negative in humans. The total number of agents is given by $N_t = N_{11} + N_{22} + N_{12} + N_{21}$.

A simple, intuitive measure of overall concordance used by Gold et al. (1989) is the proportion positive in both species, (N_{11}/N_t), plus the proportion negative in both species, (N_{22}/N_t), defined by

$$\rho = ((N_{11}+N_{22})/N_t).$$

The value of ρ ranges from 0 to 1, where $\rho=0$ and $\rho=1$ reflect perfect discordance and perfect concordance, respectively. Concordance can also be measured using the kappa (κ) statistic discussed by Viera & Garrett (2005), defined by

$$\kappa = (N_o-N_e)/(N_t-N_e),$$

where N_o and N_e denote the observed and expected total counts along the diagonal of the 2 x 2 matrix, with $N_o = N_{11}+N_{22}$ and $N_e = (N_{1.}N_{.1}/N_t) + (N_{2.}N_{.2}/N_t)$. This statistic measures concordance as slight (0.01-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-0.99). Values of $\kappa < 0$ correspond to less than chance agreement (Viera & Garrett, 2005). Since these two concordance measures are related by the formula

$$\kappa = (N_t\rho - N_e)/(N_t-N_e),$$

they provide equivalent information on concordance, albeit on a different scale of measurement.

Although the above statistical measures of concordance were considered by the Working Group (WG), the simpler measures of concordance in Supplemental Table 6 (all animals) and Supplemental Table 7 (mice and rats) were used as the basis for evaluating concordance between animal and human tumour sin the present analysis.

References

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Supplemental Table 7. Concordance between Tumours seen in Humans and Rodents (Mice and Rats) for 60 Group-1 Agents by Organ and Tissue System/Tumour Site

Supplemental Table 6. Concordance between Tumours seen in Humans and Animals for 60 Group-1 Agents by Organ and Tissue System/Tumour Site

Organ and Tissue System (Organ System No.)[1] *Tissue Site (Anatomical Site No.)* [1]	Humans	Animals[2]	Both	Overlap (%)[3]	Animal/Human Overlap (%)[4]	Human/Animal Overlap (%)[5]
Upper Aerodigestive Tract (1)	9	9	4	28.6	44.4	44.4
Nasal cavity and paranasal sinuses (1)	3	3	0	0.0	0.0	0.0
Nasopharynx (2)	3	1	1	33.3	33.3	100.0
Oral cavity (3)	4	6	2	25.0	50.0	33.3
Pharynx (4)	2	0	0	N/A	N/A	N/A
Tongue (5)	0	1	0	N/A	N/A	N/A
Salivary gland (7)	1	0	0	N/A	N/A	N/A
Respiratory System (2)	21	22	16	59.3	76.2	72.7
Larynx (9)	3	1	1	33.3	33.3	100.0
Lung (10)	20	22	16	61.5	80.0	72.7
Mesothelium (3)	2	2	2	100.0	100.0	100.0
Mesothelium (12)	2	2	2	100.0	100.0	100.0
Digestive Tract (4)	6	6	2	20.0	33.3	33.3
Oesophagus (14)	5	0	0	N/A	N/A	N/A
Stomach (15)	3	5	1	14.3	33.3	20.0
Intestine (including colon and rectum) (16)	3	1	0	0.0	0.0	0.0
Digestive Organs (5)	8	14	4	22.2	50.0	28.6
Liver parenchyma and bile ducts (17)	7	14	4	23.5	57.1	28.6
Pancreas NOS (18)	2	0	0	N/A	N/A	N/A
Gall bladder (19)	1	0	0	N/A	N/A	N/A
Nervous System and Eye (6)	2	0	0	N/A	N/A	N/A
Brain and spinal cord (CNS) (20)	1	0	0	N/A	N/A	N/A
Eye (22)	1	0	0	N/A	N/A	N/A
Endocrine System (7)	2	3	2	66.7	100.0	66.7
Thyroid, follicular epithelium (23)	2	2	2	100.0	100.0	100.0
Adrenal gland (medulla, cortex, NOS) (24)	0	1	0	N/A	N/A	N/A
Pituitary (25)	0	1	0	N/A	N/A	N/A
Kidney (8)	3	5	2	33.3	66.7	40.0
Kidney (renal cortex, renal medulla, kidney NOS) (26)	3	5	2	33.3	66.7	40.0
Urothelium (9)	10	7	7	70.0	70.0	100.0
Urothelium (renal pelvis or ureter or urinary bladder) (27)	10	7	7	70.0	70.0	100.0
Lymphoid and Haematopoietic Tissues (10)	12	10	7	46.7	58.3	70.0
Haematopoietic tissue (28)	10	2	2	20.0	20.0	100.0
Lymphoid tissue (29)	2	10	1	9.1	50.0	10.0
Skin (11)	11	16	7	35.0	63.6	43.8
Skin and adnexae (30)	9	16	6	31.6	66.7	37.5
Cutaneous melanocytes (31)	3	0	0	N/A	N/A	N/A
Connective Tissues (12)	6	14	6	42.9	100.0	42.9
Soft connective tissue (32)	0	9	0	N/A	N/A	N/A
Blood vasculature (endothelium) (33)	1	0	0	N/A	N/A	N/A
Hard connective tissue (bone, cartilage) (34)	5	5	4	66.7	80.0	80.0
Female Breast, Female Reproductive Organs and Reproductive Tract (13)	8	9	4	30.8	50.0	44.4
Breast (35)	4	7	1	10.0	25.0	14.3
Ovary (36)	3	1	0	0.0	0.0	0.0
Uterine cervix (37)	3	3	2	50.0	66.7	66.7
Uterus (38)	2	3	1	25.0	50.0	33.3
Vulva/vagina (39)	1	0	0	N/A	N/A	N/A
Other Groupings (15)	2	4	0	0.0	0.0	0.0
All cancers combined (43)	1	0	0	N/A	N/A	N/A
All solid cancers (44)	1	0	0	N/A	N/A	N/A
Exocrine glands NOS (47)	0	4	0	N/A	N/A	N/A

[1] Systems/sites in the anatomcially based tumour nomenclature system (see Supplemental Tables 1 and 4) lacking sufficient evidence in both humans and animals not shown.
  (For example, there was insufficient evidence of tumours of the male reportuctive tract in both humans and animals.)

[2] 'Animals' includes mice, rats, monkeys, dogs, and hamsters

[3] Percentage overlap calculated as $(N_b/(N_h+N_a-N_b))\times100\%$, where N_h, N_a, and N_b denote the number of agents with sufficient evidence in humans, animals,
  or both humans and animals, respectively.

[4] Percentage overlap calculated as $(N_b/N_h)\times100\%$.

[5] Percentage overlap calculated as $(N_b/N_a)\times100\%$.

  N/A: Calculation of overlap not possible when no agents demonstrate the tumour site of interest in either humans or animals (or both).

Supplemental Table 7. Concordance between Tumours seen in Humans and Rodents for 60 Group-1 Agents by Organ and Tissue System/Tumour Site

Organ and Tissue System (Organ System No.)[1] _Tissue Site (Anatomical Site No.)_ [1]	Humans	Rodents[2]	Both	Overlap (%)[3]	Animal/Human Overlap (%)[4]	Human/Animal Overlap (%)[5]
Nasal cavity and paranasal sinuses (1)	3	3	0	0.0	0.0	0.0
Nasopharynx (2)	3	1	1	33.3	33.3	100.0
Oral cavity (3)	4	6	2	25.0	50.0	33.3
Pharynx (4)	2	0	0	N/A	N/A	N/A
Tongue (5)	0	1	0	N/A	N/A	N/A
Salivary gland (7)	1	0	0	N/A	N/A	N/A
Respiratory System (2)	21	22	16	59.3	76.2	72.7
Larynx (9)	3	0	0	0.0	0.0	N/A
Lung (10)	20	22	16	61.5	80.0	72.7
Mesothelium (3)	2	2	2	100.0	100.0	100.0
Mesothelium (12)	2	2	2	100.0	100.0	100.0
Digestive Tract (4)	6	5	1	10.0	16.7	20.0
Oesophagus (14)	5	0	0	N/A	N/A	N/A
Stomach (15)	3	4	1	16.7	33.3	25.0
Intestine (including colon and rectum) (16)	3	1	0	0.0	0.0	0.0
Digestive Organs (5)	8	13	3	16.7	37.5	23.1
Liver parenchyma and bile ducts (17)	7	13	3	17.6	42.9	23.1
Pancreas NOS (18)	2	0	0	N/A	N/A	N/A
Gall bladder (19)	1	0	0	N/A	N/A	N/A
Nervous System and Eye (6)	2	0	0	N/A	N/A	N/A
Brain and spinal cord (CNS) (20)	1	0	0	N/A	N/A	N/A
Eye (22)	1	0	0	N/A	N/A	N/A
Endocrine System (7)	2	3	2	66.7	100.0	66.7
Thyroid, follicular epithelium (23)	2	2	2	100.0	100.0	100.0
Adrenal gland (medulla, cortex, NOS) (24)	0	1	0	N/A	N/A	N/A
Pituitary (25)	0	1	0	N/A	N/A	N/A
Kidney (8)	3	2	1	25.0	33.3	50.0
Kidney (renal cortex, renal medulla, kidney NOS) (26)	3	2	1	25.0	33.3	50.0
Urothelium (9)	10	6	6	60.0	60.0	100.0
Urothelium (renal pelvis or ureter or urinary bladder) (27)	10	6	6	60.0	60.0	100.0
Lymphoid and Haematopoietic Tissues (10)	12	10	7	46.7	58.3	70.0
Haematopoietic tissue (28)	10	2	2	20.0	20.0	100.0
Lymphoid tissue (29)	2	10	1	9.1	50.0	10.0
Skin (11)	11	16	7	35.0	63.6	43.8
Skin and adnexae (30)	9	16	6	31.6	66.7	37.5
Cutaneous melanocytes (31)	3	0	0	N/A	N/A	N/A
Connective Tissues (12)	6	13	5	35.7	83.3	38.5
Soft connective tissue (32)	0	9	0	N/A	N/A	N/A
Blood vasculature (endothelium) (33)	1	0	0	N/A	N/A	N/A
Hard connective tissue (bone, cartilage) (34)	5	4	3	50.0	60.0	75.0
Female Breast, Female Reproductive Organs and Reproductive Tract (13)	8	9	4	30.8	50.0	44.4
Breast (35)	4	8	2	20.0	50.0	25.0
Ovary (36)	3	1	0	0.0	0.0	0.0
Uterine cervix (37)	3	2	1	25.0	33.3	50.0
Uterus (38)	2	2	1	33.3	50.0	50.0
Vulva/vagina (39)	1	0	0	N/A	N/A	N/A
Other Groupings (15)	2	4	0	0.0	0.0	0.0
All cancers combined (43)	1	0	0	N/A	N/A	N/A
All solid cancers (44)	1	0	0	N/A	N/A	N/A
Exocrine glands NOS (47)	0	0	0	N/A	N/A	N/A

[1] Systems/sites in the anatomcially based tumour nomenclature system (see Supplemental Tables 1 and 4) lacking sufficient evidence in both humans and animals not shown.

(For example, there was insufficient evidence of tumours of the male reportuctive tract in both humans and animals.)

[2] 'Rodents' includes mice and rats.

[3] Percentage overlap calculated as $(N_b/(N_h+N_a-N_b))\times100\%$, where N_h, N_a, and N_b denote the number of agents with sufficient evidence in humans, animals,

or both humans and animals, respectively.

[4] Percentage overlap calculated as $(N_b/N_h)\times100\%$.

[5] Percentage overlap calculated as $(N_b/N_a)\times100\%$.

N/A: Calculation of overlap not possible when no agents demonstrate the tumour site of interest in either humans or animals (or both).