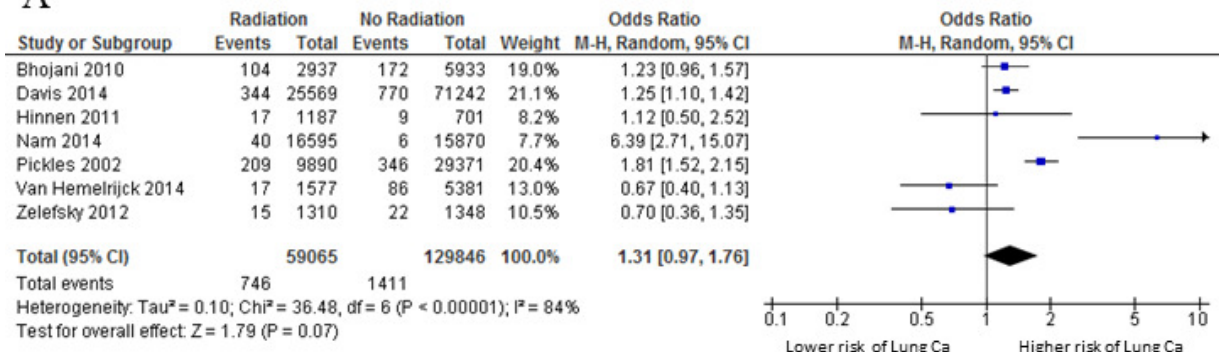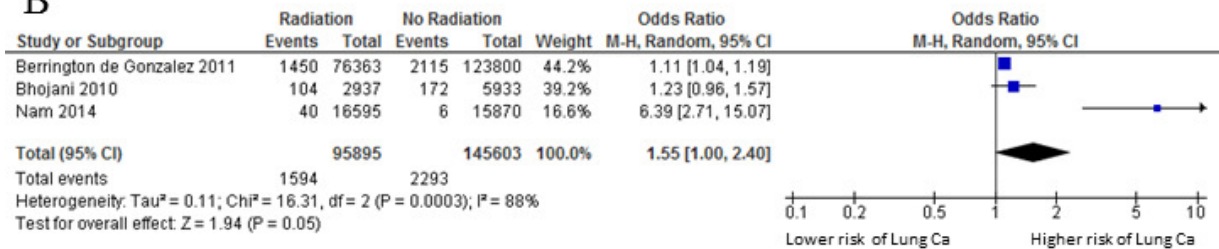**Appendix 5:** Supplementary figures [posted as supplied by author]

Figure A. Forest plots of studies assessing the risk of lung cancer following any radiotherapy compared with no radiation by (a) no restriction to lag period; (b) restriction to studies using a 5-year lag period; (c) restriction to studies using a 10-year lag period; and (d) studies reporting adjusted hazard ratios.

Figure B. Forest plots of studies assessing the risk of hematologic cancer following any radiotherapy compared with no radiation by (a) no restriction to lag period; (b) restriction to studies using a 5-year lag period; (c) restriction to studies using a 10-year lag period; and (d) studies reporting adjusted hazard ratios.
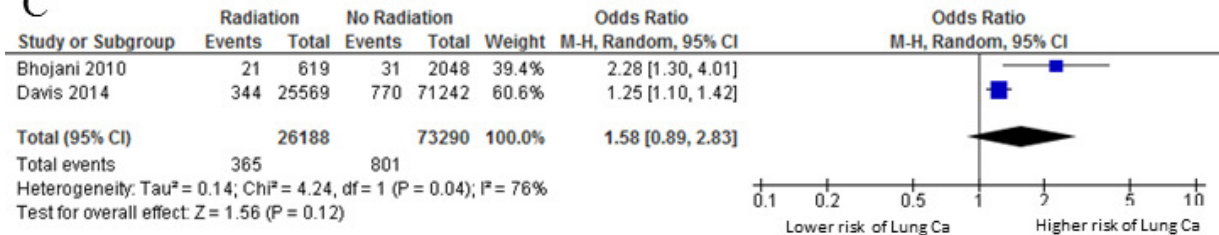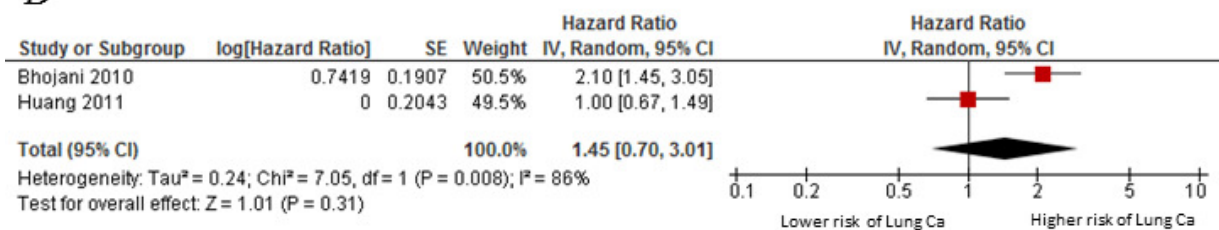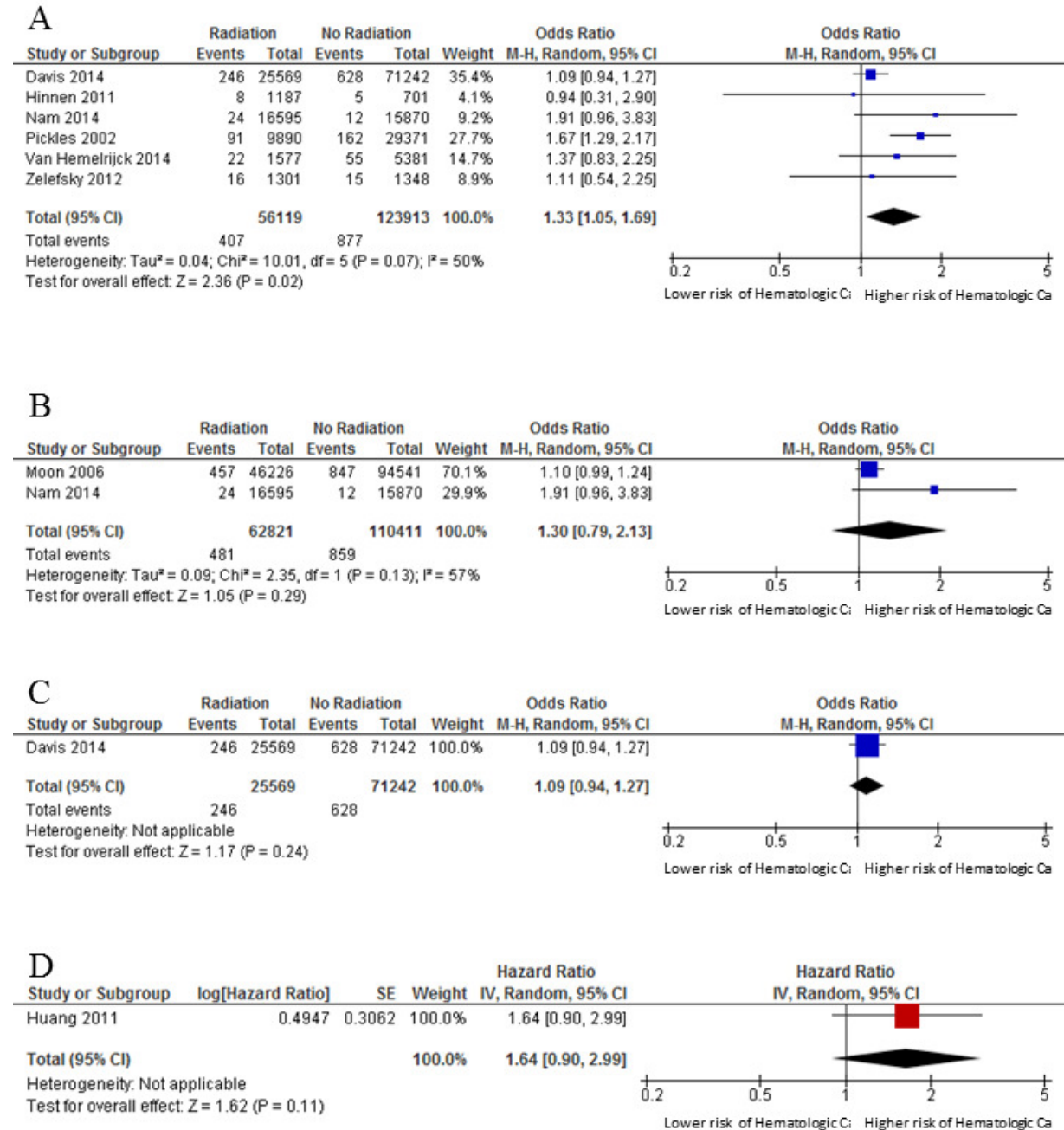
Figure C. Forest plots of studies assessing the risk of secondary cancers associated with external beam radiotherapy (EBRT) without a lag period for (a) bladder cancer; (b) colorectal cancer; (c) rectal cancer; (d) lung cancer; and (e) hematologic cancer.

A

Study or Subgroup	Radiation Events	Total	No Radiation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhojani 2010	69	3008	120	5693	20.6%	1.09 [0.81, 1.47]
Davis 2014	343	25569	506	71242	26.3%	1.90 [1.66, 2.18]
Nam 2014	17	16595	12	15870	8.7%	1.36 [0.65, 2.84]
Pickles 2002	62	9890	134	29371	20.6%	1.38 [1.02, 1.86]
Van Hemelrijck 2014	23	1577	64	5381	14.5%	1.23 [0.76, 1.99]
Zelefsky 2012	16	1310	16	1348	9.4%	1.03 [0.51, 2.07]
Total (95% CI)		57949		128905	100.0%	1.37 [1.05, 1.77]
Total events	530		852			

Heterogeneity: Tau² = 0.06; Chi² = 16.14, df = 5 (P = 0.006); I² = 69%
Test for overall effect: Z = 2.34 (P = 0.02)

Lower risk of Bladder Ca — Higher risk of Bladder Ca

B

Study or Subgroup	Radiation Events	Total	No Radiation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhojani 2010	33	3079	43	6037	12.6%	1.51 [0.96, 2.38]
Davis 2014	310	25569	557	71242	20.1%	1.56 [1.35, 1.79]
Margel 2011	26	2163	168	26830	13.5%	1.93 [1.27, 2.93]
Nam 2014	45	16595	15	15870	9.9%	2.87 [1.60, 5.16]
Pickles 2002	234	9890	319	29371	19.5%	2.21 [1.86, 2.62]
Rapiti 2008	11	264	8	870	5.5%	4.68 [1.86, 11.77]
Van Hemelrijck 2014	24	1577	97	5381	12.7%	0.84 [0.54, 1.32]
Zelefsky 2012	13	1310	9	1348	6.2%	1.49 [0.64, 3.50]
Total (95% CI)		60447		156949	100.0%	1.78 [1.38, 2.29]
Total events	696		1216			

Heterogeneity: Tau² = 0.08; Chi² = 27.86, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 4.49 (P < 0.00001)

Lower risk of Colorectal Ca — Higher risk of Colorectal Ca

C

Study or Subgroup	Radiation Events	Total	No Radiation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhojani 2010	33	3079	43	6037	21.8%	1.51 [0.96, 2.38]
Davis 2014	112	25569	142	71242	33.8%	2.20 [1.72, 2.82]
Margel 2011	26	2163	168	26830	23.8%	1.93 [1.27, 2.93]
Rapiti 2008	2	264	4	870	2.9%	1.65 [0.30, 9.07]
Van Hemelrijck 2014	7	1577	28	5381	10.1%	0.85 [0.37, 1.96]
Zelefsky 2012	7	1310	9	1348	7.6%	0.80 [0.30, 2.15]
Total (95% CI)		33962		111708	100.0%	1.64 [1.21, 2.21]
Total events	187		394			

Heterogeneity: Tau² = 0.05; Chi² = 8.85, df = 5 (P = 0.12); I² = 44%
Test for overall effect: Z = 3.23 (P = 0.001)

Lower risk of Rectal Ca — Higher risk of Rectal Ca

D

Study or Subgroup	Radiation Events	Total	No Radiation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bhojani 2010	104	2937	172	5933	20.6%	1.23 [0.96, 1.57]
Davis 2014	344	25569	770	71242	22.8%	1.25 [1.10, 1.42]
Nam 2014	40	16595	6	15870	8.6%	6.39 [2.71, 15.07]
Pickles 2002	209	9890	346	29371	22.1%	1.81 [1.52, 2.15]
Van Hemelrijck 2014	17	1577	86	5381	14.3%	0.67 [0.40, 1.13]
Zelefsky 2012	15	1310	22	1348	11.6%	0.70 [0.36, 1.35]
Total (95% CI)		57878		129145	100.0%	1.33 [0.97, 1.82]
Total events	729		1402			

Heterogeneity: Tau² = 0.11; Chi² = 36.25, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.77 (P = 0.08)

Lower risk of Lung Ca — Higher risk of Lung Ca

E

Study or Subgroup	Radiation Events	Total	No Radiation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Davis 2014	246	25569	628	71242	35.7%	1.09 [0.94, 1.27]
Nam 2014	24	16595	12	15870	10.5%	1.91 [0.96, 3.83]
Pickles 2002	91	9890	162	29371	28.9%	1.67 [1.29, 2.17]
Van Hemelrijck 2014	22	1577	55	5381	16.3%	1.37 [0.83, 2.25]
Zelefsky 2012	11	897	15	1348	8.7%	1.10 [0.50, 2.41]
Total (95% CI)		54528		123212	100.0%	1.36 [1.05, 1.77]
Total events	394		872			

Heterogeneity: Tau² = 0.04; Chi² = 9.78, df = 4 (P = 0.04); I² = 59%
Test for overall effect: Z = 2.32 (P = 0.02)

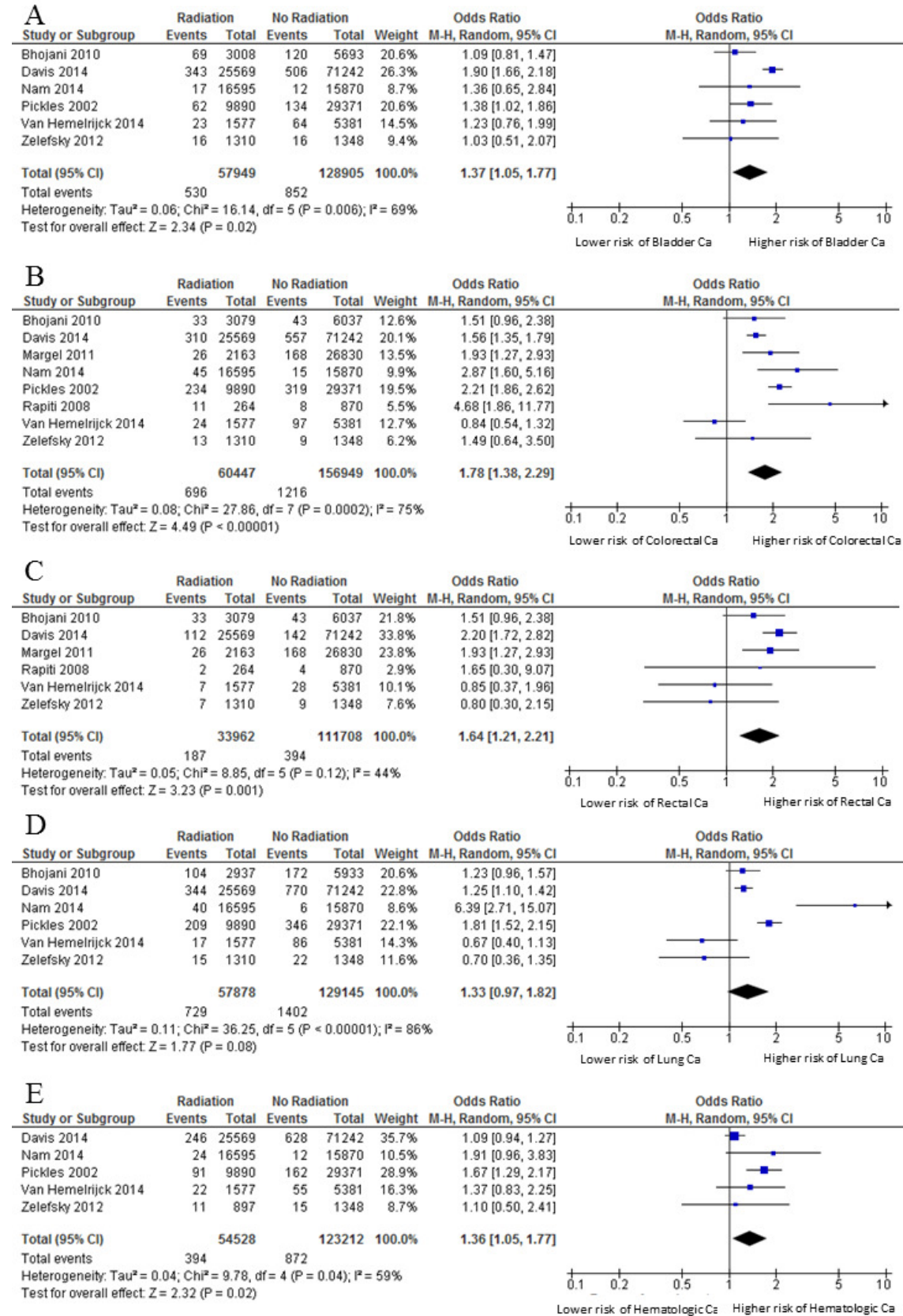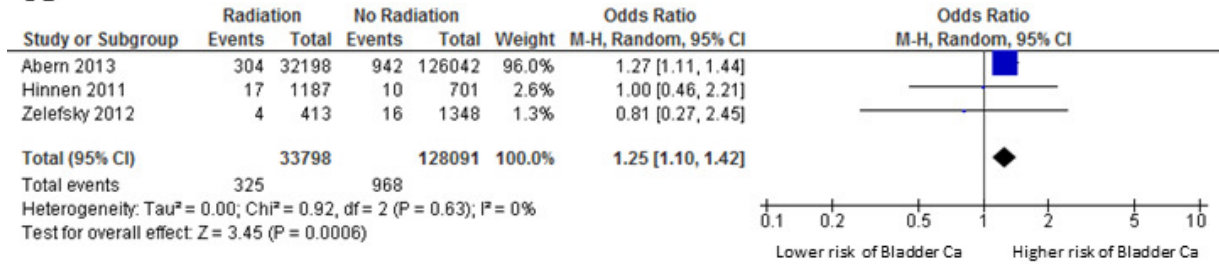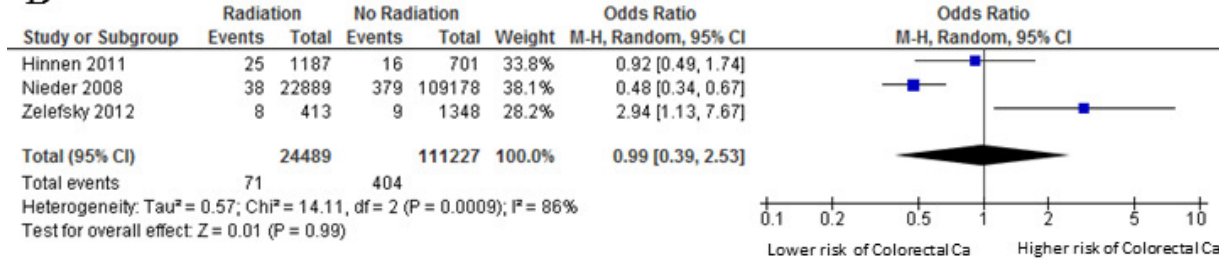Lower risk of Hematologic Ca — Higher risk of Hematologic Ca

Figure D. Forest plots of studies assessing the risk of secondary cancers associated with brachytherapy without a lag period for (a) bladder cancer; (b) colorectal cancer; (c) rectal cancer; (d) lung cancer; and (e) hematologic cancer.
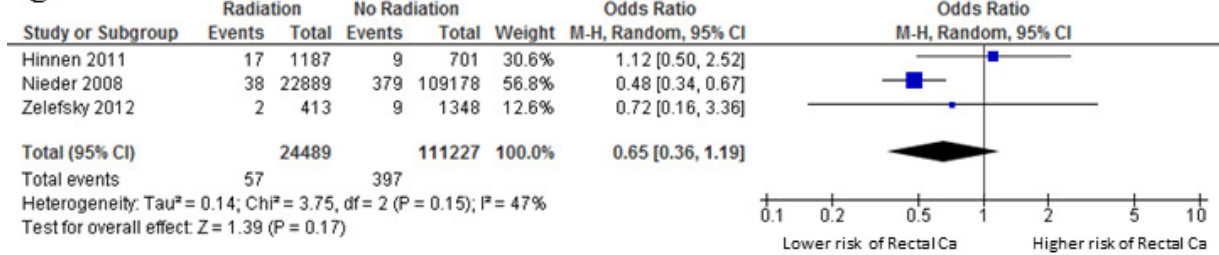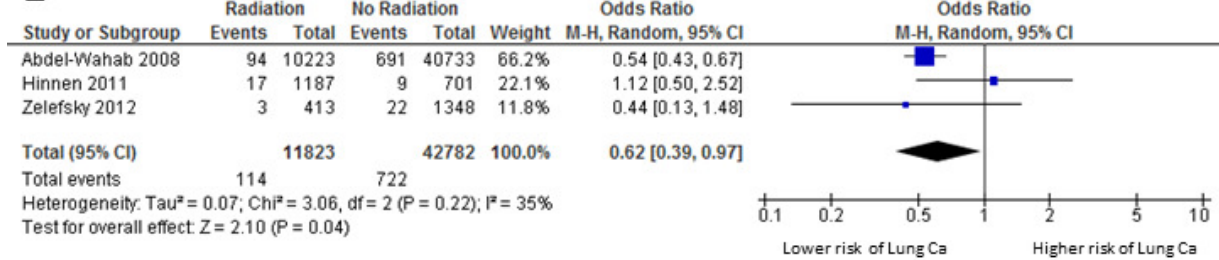
A

Study or Subgroup	Radiation Events	Radiation Total	No Radiation Events	No Radiation Total	Weight	Odds Ratio M-H, Random, 95% CI
Abern 2013	304	32198	942	126042	96.0%	1.27 [1.11, 1.44]
Hinnen 2011	17	1187	10	701	2.6%	1.00 [0.46, 2.21]
Zelefsky 2012	4	413	16	1348	1.3%	0.81 [0.27, 2.45]
Total (95% CI)		33798		128091	100.0%	1.25 [1.10, 1.42]
Total events	325		968			

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.45 (P = 0.0006)

Odds Ratio M-H, Random, 95% CI — Lower risk of Bladder Ca / Higher risk of Bladder Ca

B

Study or Subgroup	Radiation Events	Radiation Total	No Radiation Events	No Radiation Total	Weight	Odds Ratio M-H, Random, 95% CI
Hinnen 2011	25	1187	16	701	33.8%	0.92 [0.49, 1.74]
Nieder 2008	38	22889	379	109178	38.1%	0.48 [0.34, 0.67]
Zelefsky 2012	8	413	9	1348	28.2%	2.94 [1.13, 7.67]
Total (95% CI)		24489		111227	100.0%	0.99 [0.39, 2.53]
Total events	71		404			

Heterogeneity: Tau² = 0.57; Chi² = 14.11, df = 2 (P = 0.0009); I² = 86%
Test for overall effect: Z = 0.01 (P = 0.99)

Odds Ratio M-H, Random, 95% CI — Lower risk of Colorectal Ca / Higher risk of Colorectal Ca

C

Study or Subgroup	Radiation Events	Radiation Total	No Radiation Events	No Radiation Total	Weight	Odds Ratio M-H, Random, 95% CI
Hinnen 2011	17	1187	9	701	30.6%	1.12 [0.50, 2.52]
Nieder 2008	38	22889	379	109178	56.8%	0.48 [0.34, 0.67]
Zelefsky 2012	2	413	9	1348	12.6%	0.72 [0.16, 3.36]
Total (95% CI)		24489		111227	100.0%	0.65 [0.36, 1.19]
Total events	57		397			

Heterogeneity: Tau² = 0.14; Chi² = 3.75, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.39 (P = 0.17)

Odds Ratio M-H, Random, 95% CI — Lower risk of Rectal Ca / Higher risk of Rectal Ca

D

Study or Subgroup	Radiation Events	Radiation Total	No Radiation Events	No Radiation Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdel-Wahab 2008	94	10223	691	40733	66.2%	0.54 [0.43, 0.67]
Hinnen 2011	17	1187	9	701	22.1%	1.12 [0.50, 2.52]
Zelefsky 2012	3	413	22	1348	11.8%	0.44 [0.13, 1.48]
Total (95% CI)		11823		42782	100.0%	0.62 [0.39, 0.97]
Total events	114		722			

Heterogeneity: Tau² = 0.07; Chi² = 3.06, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 2.10 (P = 0.04)

Odds Ratio M-H, Random, 95% CI — Lower risk of Lung Ca / Higher risk of Lung Ca

E

Study or Subgroup	Radiation Events	Radiation Total	No Radiation Events	No Radiation Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdel-Wahab 2008	45	10223	164	40733	83.9%	1.09 [0.79, 1.52]
Hinnen 2011	8	1187	5	701	7.3%	0.94 [0.31, 2.90]
Zelefsky 2012	5	413	15	1348	8.8%	1.09 [0.39, 3.01]
Total (95% CI)		11823		42782	100.0%	1.08 [0.80, 1.46]
Total events	58		184			

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)

Odds Ratio M-H, Random, 95% CI — Lower risk of Hematologic Ca / Higher risk of Hematologic Ca