Online-Only references

Supplementary Table S1. Criteria for evaluation of the methodological quality of studies

Supplementary Table S2. Characteristics of eligible studies

Supplementary Table S3. Criteria used to define chemotherapy-induced amenorrhea in eligible studies

Online-Only references

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**Table S1. Criteria for evaluation of the methodological quality of studies**

|  |
| --- |
| **Sample Definition and Selection**1. Is the study design prospective, retrospective, or not applicable?2. Are critical inclusion/exclusion criteria clearly stated?3. Are the inclusion/exclusion criteria measured using valid and reliable measures?4. Was the sample size sufficiently large to detect a clinically significant difference (> 100 patients) |
| **Source of information**5. Are interventions/exposures (variables tested as potential risk factors for amenorrhea) assessed using valid and reliable measures, implemented consistently across all study participants? 6. Are outcomes (presence of amenorrhea) assessed using valid and reliable measures, implemented consistently across all study participants? |
| **Follow-up**7. Is the length of follow-up the same for all groups?8. Is the length of time following the intervention/exposure sufficient to support the evaluation ofprimary outcomes (at least 12 months)?9. Did attrition from any group exceed > 30%? 10. Did attrition differ between groups by more than 20%? |
| **Analysis Comparability / Outcome**11. Were the important confounding and effect modifying variables taken into account in thedesign and/or analysis?12. In cases of high loss to follow-up (or differential loss to follow-up), is the impact assessed (e.g.,through sensitivity analysis or other adjustment method)?13. Are the statistical methods used to assess the primary benefit outcomes appropriate to thedata?14. Are results believable taking study limitations into consideration? |

**Table S2. Characteristics of eligible studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author (ref)** | **Country** | **Study type** | **Follow-up (median, months)** | **Sample size** | **Multivariate analysis for risk factors** | **Study quality** |
| Abusief (1) | USA | Retrospective cohort | 33 | 431 | Yes | 11 |
| Andersson (2) | Denmark | RCT | 146 | 634 | No | NA |
| Badaway (3) | Egypt | RCT | NR | 78 | No | NA |
| Beex (4) | The Netherlands | Retrospective cohort | 37 | 77 | No | 3 |
| Berliere (5) | Multinational | Retrospective cohort | 79 | 154 | No | 6 |
| Bianco (6) | Italy | Retrospective cohort | 69 | 221 | No | 5 |
| Boccardo (7) | Italy | RCT | 40 | 336 | No | NA |
| Bonadonna (8) | Italy | RCT | 22 | 90 | No | NA |
| Brincker (9) | Denmark | RCT | 64 | 847 | No | NA |
| Campora (10) | Italy | Retrospective cohort | 72 | 108 | No | 5 |
| Colleoni (11) | Italy | RCT | 100 | 344 | No | NA |
| Davis (12) | USA | Retrospective cohort | NR | 159 | No | 4 |
| Del Mastro (13) | Italy | RCT | NR | 133 | Yes | NA |
| Di Cosimo (14) | Italy | Retrospective cohort | NR | 111 | Yes | 7 |
| Fornier (15) | USA | Retrospective cohort | 38 | 166 | No | 8 |
| Ganz (16) | Multinational | RCT | NR | 2149 | No | NA |
| Gerber (17) | Germany | RCT | NR | 60 | No | NA |
| Goldhirsch (18) | Multinational | RCT | 48 | 1127 | No | NA |
| Goodwin (19) | Canada | Prospective cohort | 12 | 183 | Yes | 12 |
| Han (20) | South Korea | Prospective cohort | 40 | 285 | Yes | 14 |
| Hortobagyi (21) | USA | Retrospective cohort | NR | 69 | No | 6 |
| Howell (22) | UK | RCT | NR | 81 | No | NA |
| IBCSG (23) | Multinational | RCT | 70 | 1065 | No | NA |
| IBCSG (24) | Multinational | RCT | 84 | 360 | No | NA |
| Kil (25) | South Korea | Retrospective cohort | 54 | 165 | No | 5 |
| Jonat (26) | Multinational | RCT | 72 | 802 | No | NA |
| Jung (27) | South Korea | Retrospective cohort | 110 | 241 | Yes | 9 |
| Lee (28) | South Korea | Retrospective cohort | 37 | 326 | Yes | 10 |
| Lower (29) | USA | Retrospective cohort | 24 | 109 | No | 6 |
| Ludwig BCSG (30) | Multinational | RCT | 48 | 340 | No | NA |
| Marini (31) | Multinational | RCT | 156 | 491 | No | NA |
| Martin (32) | Multinational | RCT | 55 | 823 | No | NA |
| Mehta (33) | USA | Prospective cohort | NR | 70 | No | 5 |
| Meng (34) | China | Retrospective cohort | 27 | 73 | No | 5 |
| Minisini (35) | Italy | Retrospective cohort | 34 | 145 | Yes | 8 |
| Munster (36) | USA | RCT | 18 | 21 | No | NA |
| Najafi (37) | Iran | Retrospective cohort | 36 | 226 | Yes | 8 |
| Narmadha (38) | India | Cross sectional | NR | 50 | No | 4 |
| Okanami (39) | Japan | Cross sectional | 28 | 66 | Yes | 6 |
| Padmanabhan (40) | UK | RCT | 47 | 35 | No | NA |
| Pagani (41) | Multinational | RCT | 60 | 1196 | No  | NA |
| Partridge (42) | Multinational | RCT | 156 + 228 | 767 | No | NA |
| Parulekar (43) | Canada | Retrospective cohort | 106 | 328 | No | 7 |
| Pérez-Fildago (44) | Spain | Retrospective cohort | NR | 305 | No | 7 |
| Petrek (45) | USA | Prospective cohort | 45 | 595 | Yes | 13 |
| Poikonen (46) | Finland | Prospective cohort | 72 | 116 | No | 7 |
| Pourali (47) | Iran | Cross sectional | NR | 119 | No | 5 |
| Reh (48) | USA | Prospective cohort | 28 | 41 | No | 7 |
| Reyno (49) | Canada | RCT | NR | 95 | No | NA |
| Richards (50) | UK | RCT | 96 | 90 | No | NA |
| Roché (51) | France | RCT | 84 | 169 | No | NA |
| Rose (52) | USA | Retrospective cohort | NR | 38 | No | 6 |
| Rosendahl (53) | Multinational | RCT | NR | 836 | No | NA |
| Ruddy (54) | USA | Prospective cohort | NR | 124 | Yes | 9 |
| Saarto (55) | Finland | Prospective cohort | NR | 57 | No | 7 |
| Samaan (56) | USA | Prospective cohort | NR | 55 | No | 5 |
| Shapiro (57) | USA | Prospective cohort | NR | 49 | No | 7 |
| Su (58) | USA | Prospective cohort | 62 | 111 | Yes | 8 |
| Sukumvanich (59) | USA | Prospective cohort | NR | 439 | Yes | 12 |
| Sverrisdottir (60) | Multinational | RCT | NR | 31 | No | NA |
| Swain (61) | USA | RCT | 73 | 2343 | No | NA |
| Tancini (62) | Italy | RCT | 22 | 287 | No | NA |
| Tham (63) | USA | Cross sectional | NR | 191 | Yes | 8 |
| Tiong (64) | Malaysia | Cross sectional | NR | 87 | No | 7 |
| Toma (65) | Italy | Retrospective cohort | NR | 146 | No | 5 |
| Tormey (66) | USA | RCT | 92 | 553 | No | NA |
| Valagussa (67) | Italy | Retrospective cohort | 44 | 494 | No | 5 |
| Vanhuyse (68) | France | Retrospective cohort | 108 | 130 | No | 6 |
| Vehmanen (98) | Finland | RCT | 36 | 111 | No | NA |
| Vehmanen (70) | Finland | Prospective cohort | 60 | 73 | No | 8 |
| Venturini (71) | Italy | RCT | 125 | 503 | No | NA |
| Yoo (72) | South Korea | Prospective cohort | 18 | 312 | Yes | 12 |
| Yu (73) | USA | Prospective cohort | NR | 26 | No | 7 |
| Zekri (74) | UK | Retrospective cohort | 39 | 26 | No | 4 |
| Zhou (75) | China | Cross sectional | 39 | 170 | Yes | 7 |

Abbreviations: RCT, Randomized controlled trial; NA, Not Applicable; NR, Not Reported.

**Table S3. Criteria used to define chemotherapy-induced amenorrhea in eligible studies**

|  |  |
| --- | --- |
| **Definition criteria** | ***N* of studies (%)** |
| *Different duration from end of chemotherapy* No menstrual bleeding for 6 months No menstrual bleeding for 12 months  No menstrual bleeding for different durations within the same study | 4 (5)7 (9)3 (4) |
| *Different duration from start of chemotherapy* No menstrual bleeding within 6 months No menstrual bleeding within 10 months No menstrual bleeding within at least 12 months No menstrual bleeding for different durations within the same study | 5 (7)1 (1)9 (12)3 (4) |
| *Different duration from randomization* No menstrual bleeding within 6 months No menstrual bleeding within 7-9 months No menstrual bleeding within at least 12 months No menstrual bleeding for different durations within the same study | 1 (1)2 (3)1 (1)1 (1) |
| *Definition based on both duration of amenorrhea and interval from chemotherapy*  No menstrual bleeding during chemotherapy and at least 3 months No menstrual bleeding during chemotherapy and at least 6 months No menstrual bleeding during chemotherapy and during follow up No menstrual bleeding within 3 months from start of chemotherapy and for at least 3 months No menstrual bleeding within 9 months from surgery and for at least 3 months No menstrual bleeding within 12 months from start of chemotherapy for at least 1 month No menstrual bleeding within 12 months from start of chemotherapy for at least 3 months No menstrual bleeding within 12 months from start of chemotherapy for at least 6 months No menstrual bleeding within 12 months from start of chemotherapy for at least 12 months No menstrual bleeding within 12 months from end of chemotherapy for at least 6 months | 4 (5)1 (1)2 (3)2 (3)1 (1)1 (1)2 (3)4 (5)2 (3)2 (3) |
| *No menstrual bleeding during chemotherapy* | 2 (3) |
| *No clear definition* | 15 (20) |
| *Laboratory criteria* Rise of gonadotropins | 3 (4) |
| *Recovery* No recovery of menstrual bleeding Not included in the definition | 5 (7)70 (93) |